Updates in neuroncologia clinica
Neurochirurgia

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Introduzione

- *Classe eterogenea di tumori*
- *Non esistono gliomi benigni (ecc. a. pilocitico)*
- *Malattia d'organo ?*
- *Storia naturale variabile tra i differenti istotipi*
- *Assenza di evidenze classe I*
- *Ruolo della chirurgia differente tra i "low grade" e gli "high grade"*
- *Approccio multidisciplinare*

Cerebral Glioblastomas Can Be Cured!

Paul C. Bucy, M.D., H. R. Oberhill, M.D., Edir B. Siqueira, M.D., Ph.D., H. M. Zimmerman, M.D., and Richard K. Jelsma, M.D.

Northwestern Memorial Hospital and Northwestern University Medical School, Chicago, Illinois

In 1959, a 30-year-old man underwent the removal of a glioblastoma multiforme from the right parietal lobe of his brain. After the operation, he received x-ray therapy. He made a complete recovery. Today, over 25 years later, he is alive and well and is regularly employed full-time. If glioblastomas and other cerebral gliomas are removed completely, the patients can be cured of their tumors. (*Neurosurgery* 16:714–717, 1985)

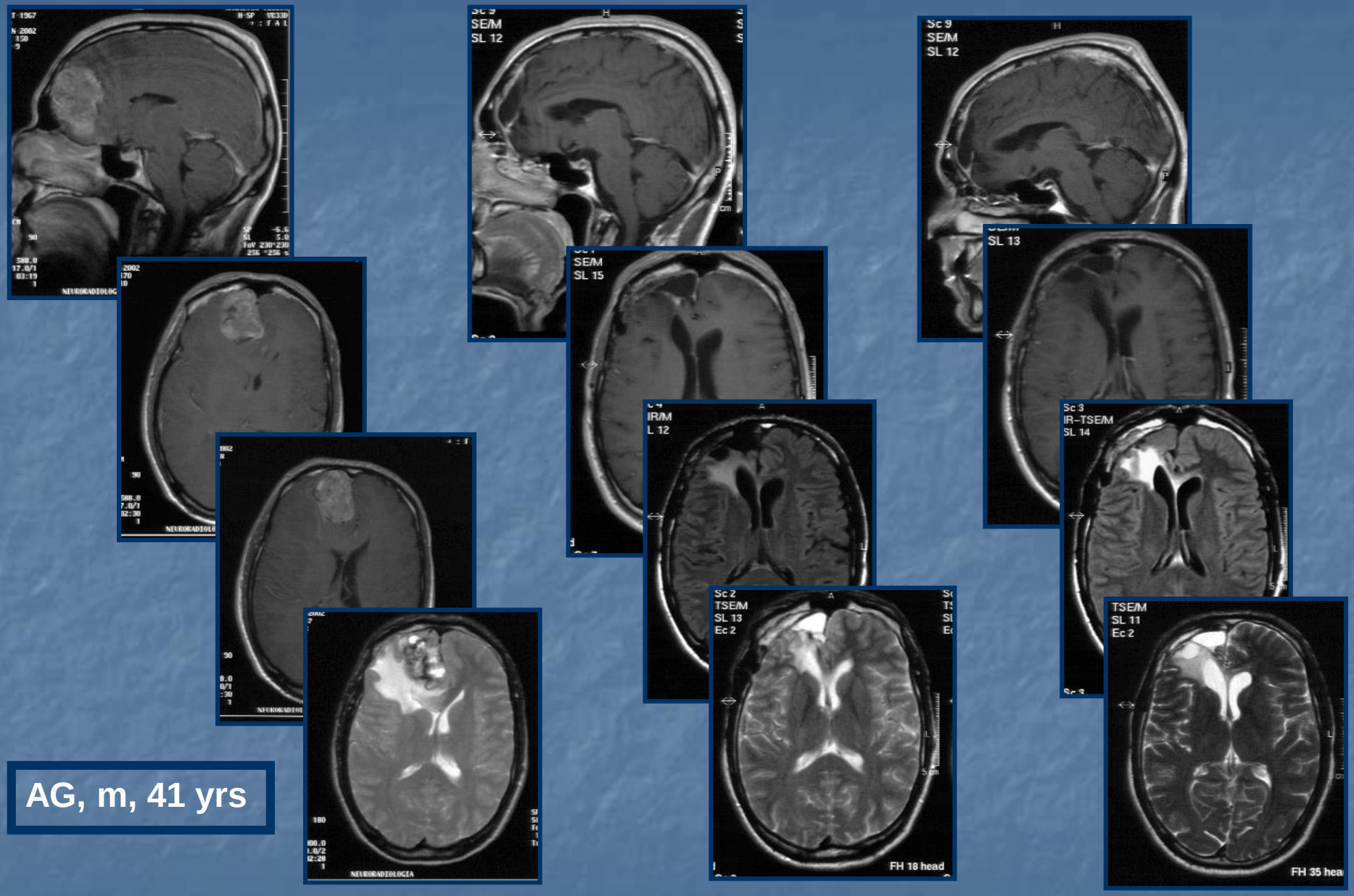
Infatti, se i tumori gliali:

crescono per estensione locale

recidivano quasi esclusivamente localmente

non metastatizzano quasi mai

TEORICAMENTE CANDIDATI IDEALI ALLA GUARIGIONE CHIRURGICA, MA…



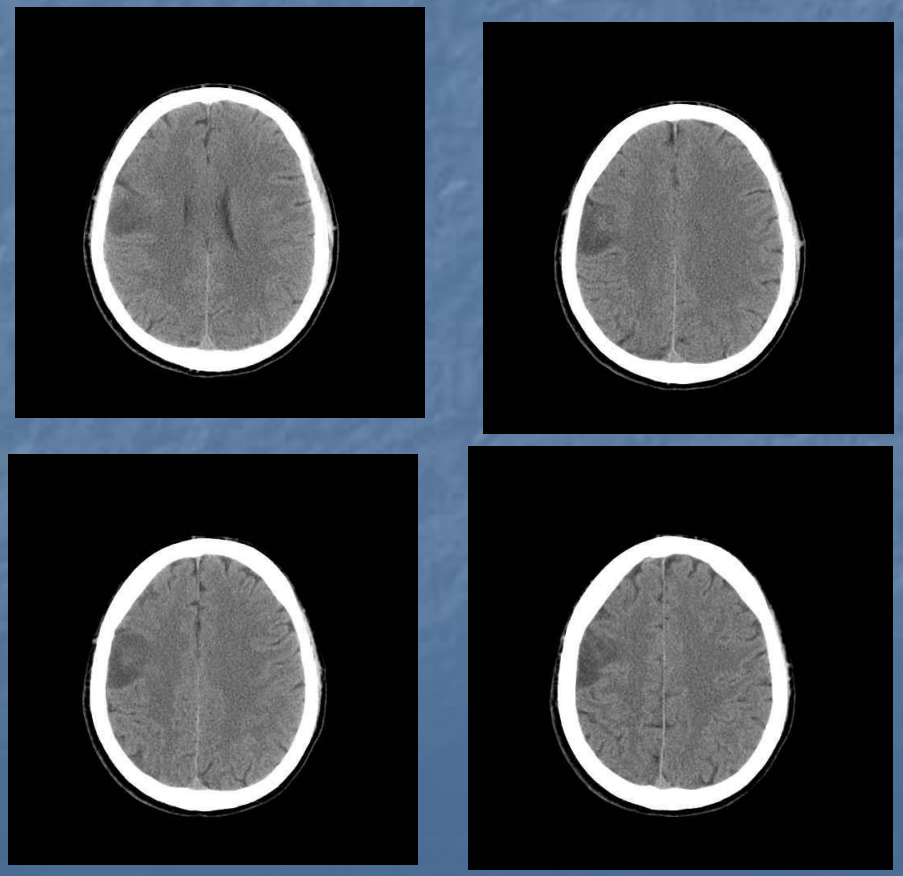
AG, m, 41 yrs

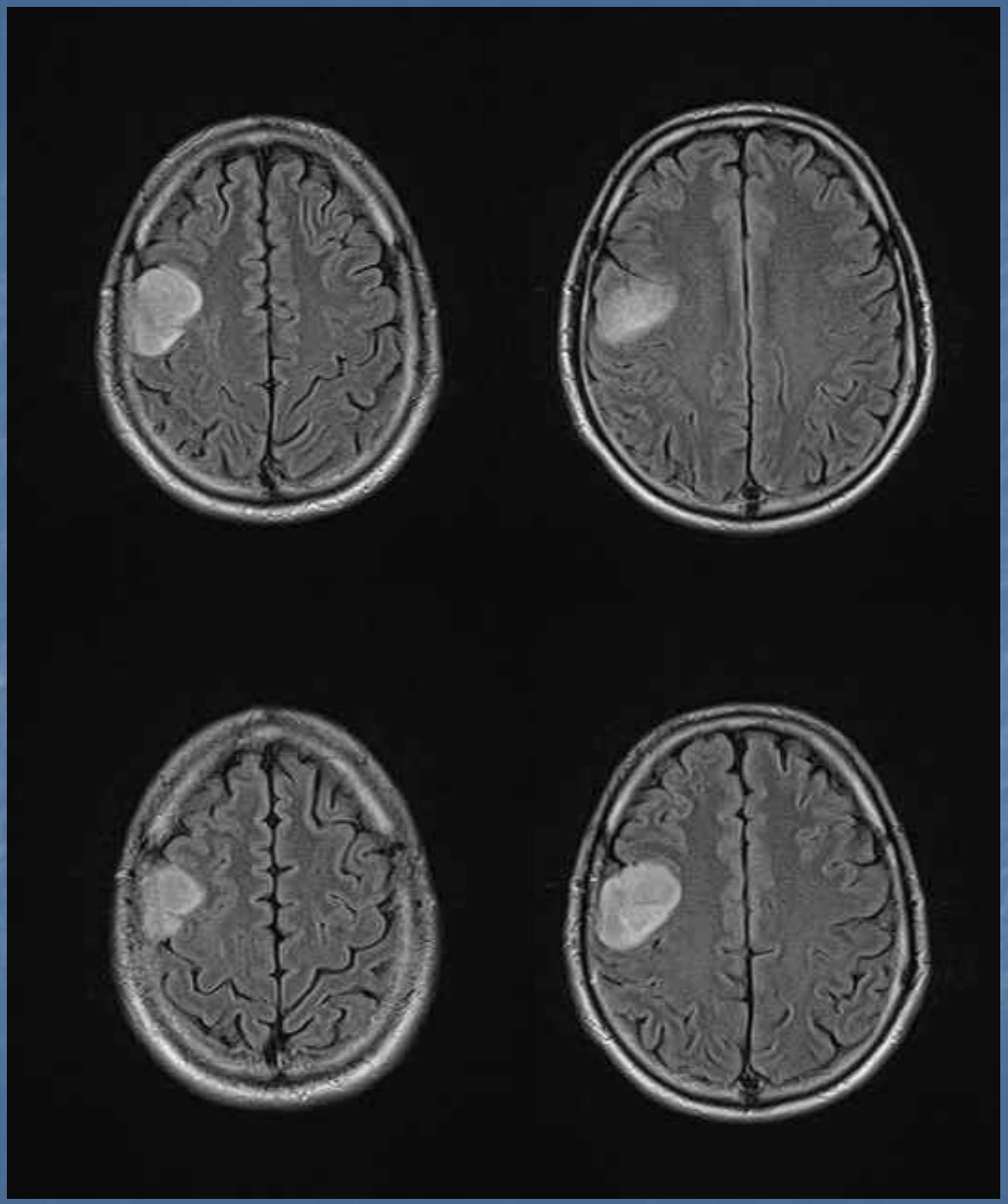
01.2002 **02.2006** **09.2010**

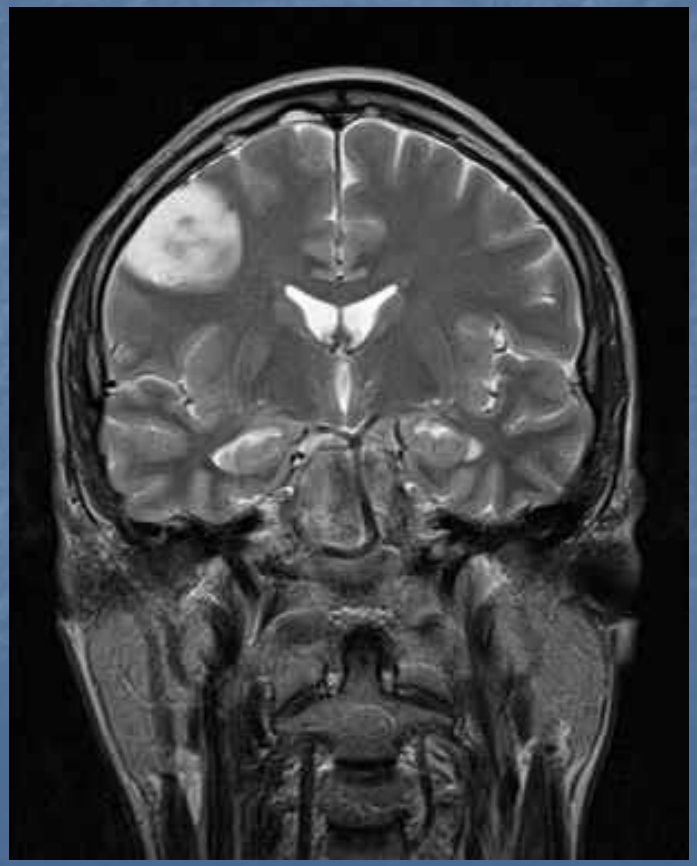
Maschio 45 anni

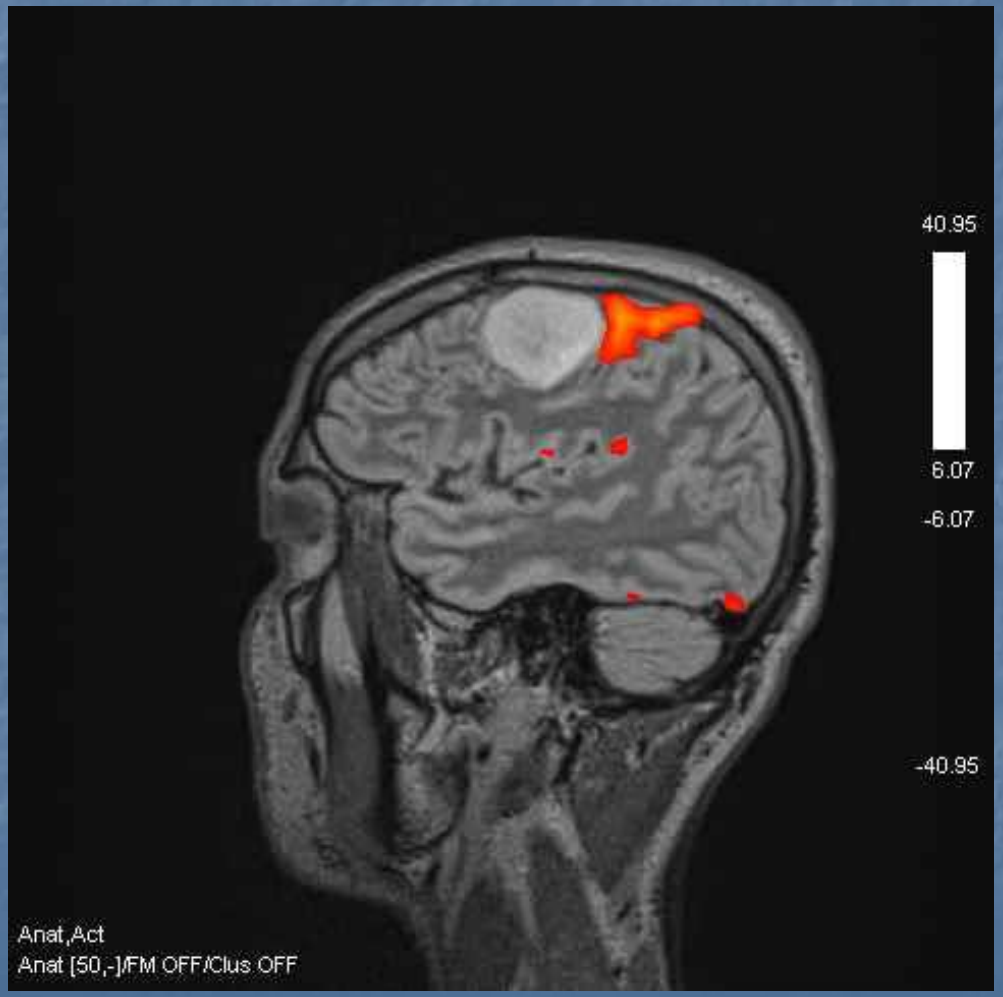
Crisi morfeica generalizzata

Accesso in PS



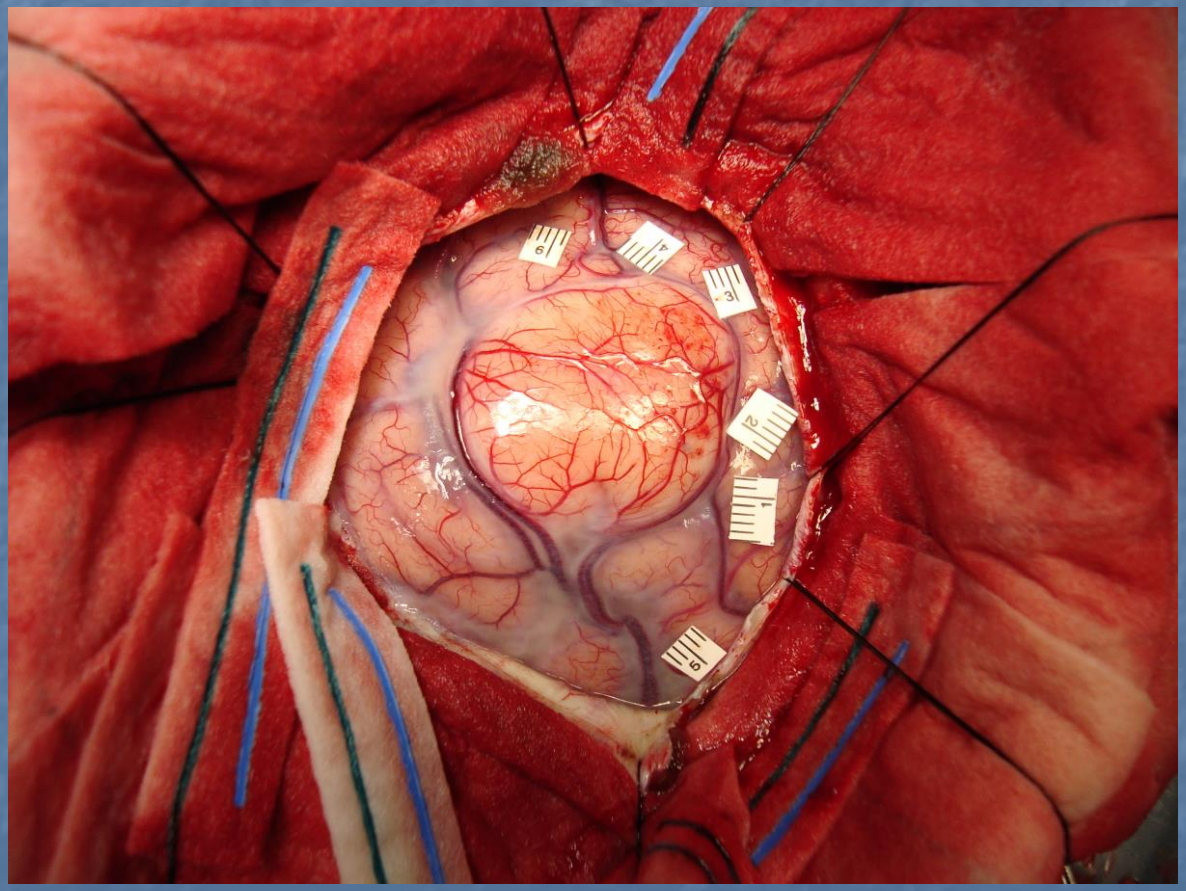






RM Bolt

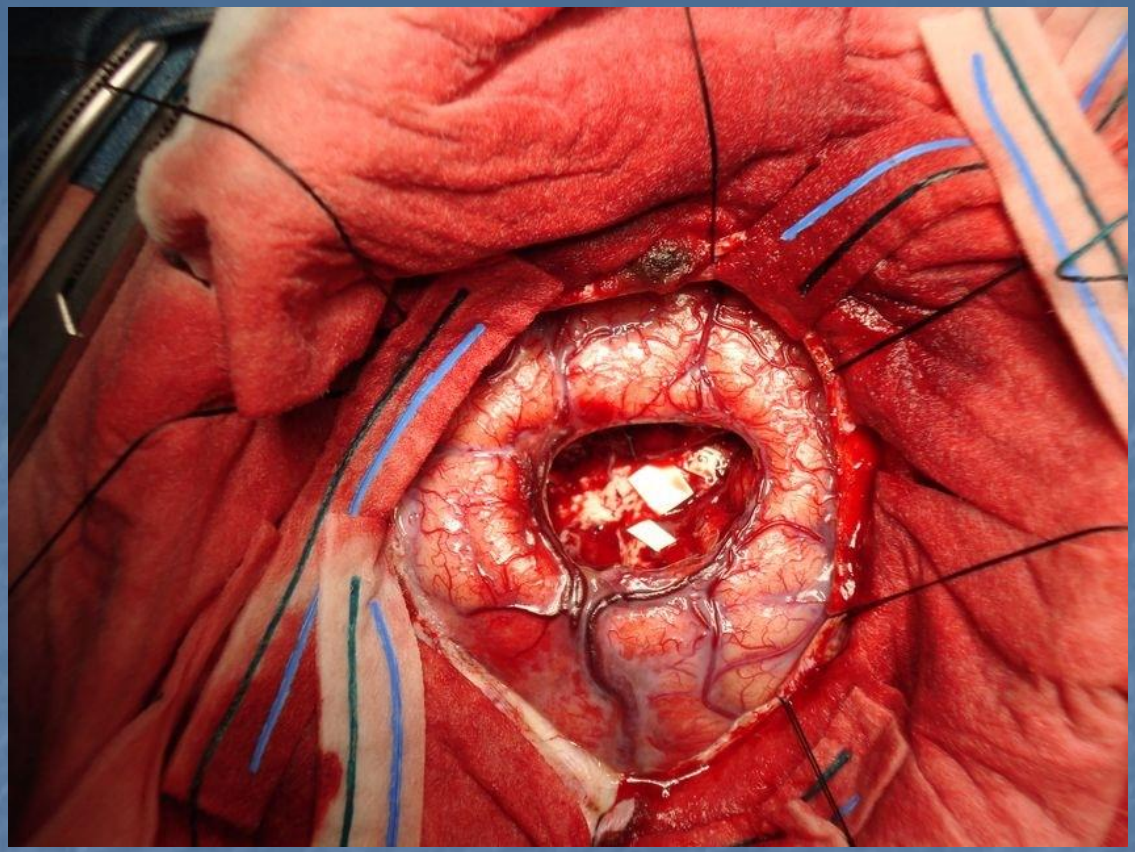
Awake surgery



1. Area sensitiva indice e medio
2. Area sensitiva pollice
3. Area sensitiva labbro
4. Area sensitiva bocca
5. Area motoria mano
6. Disartria motoria

Area motoria faciale e deviazione esterna dell'occhio

(Fascio cortico spinale)

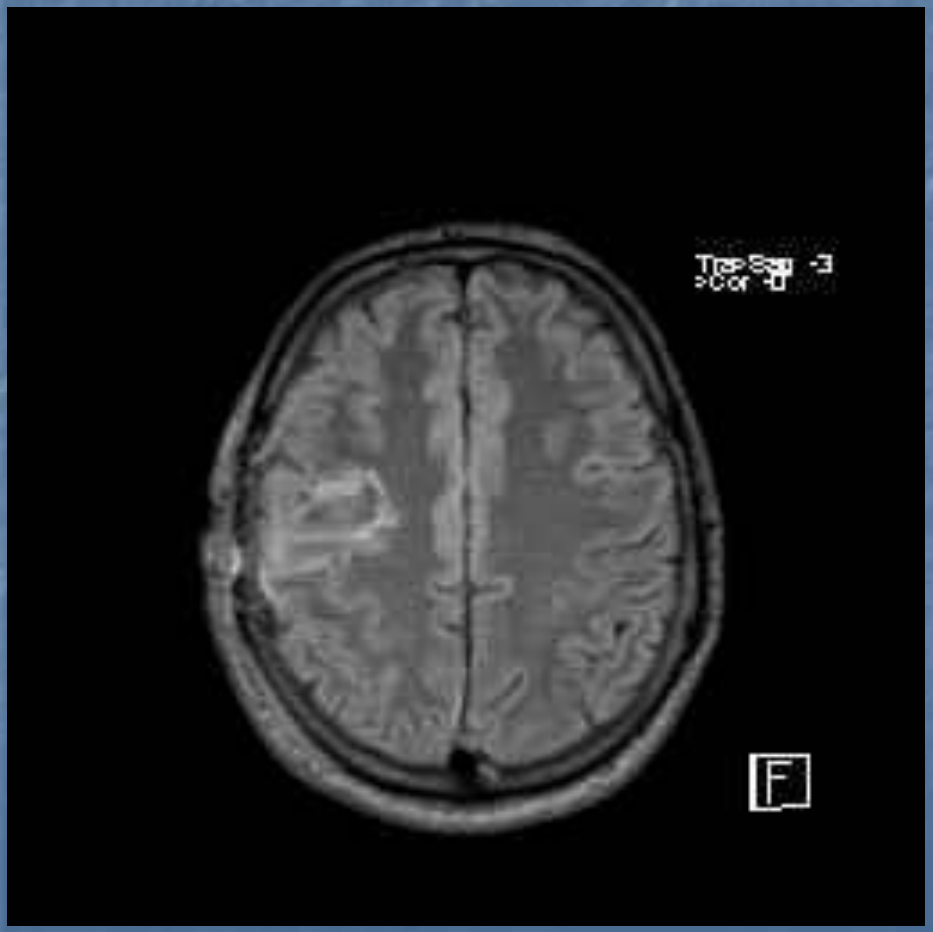


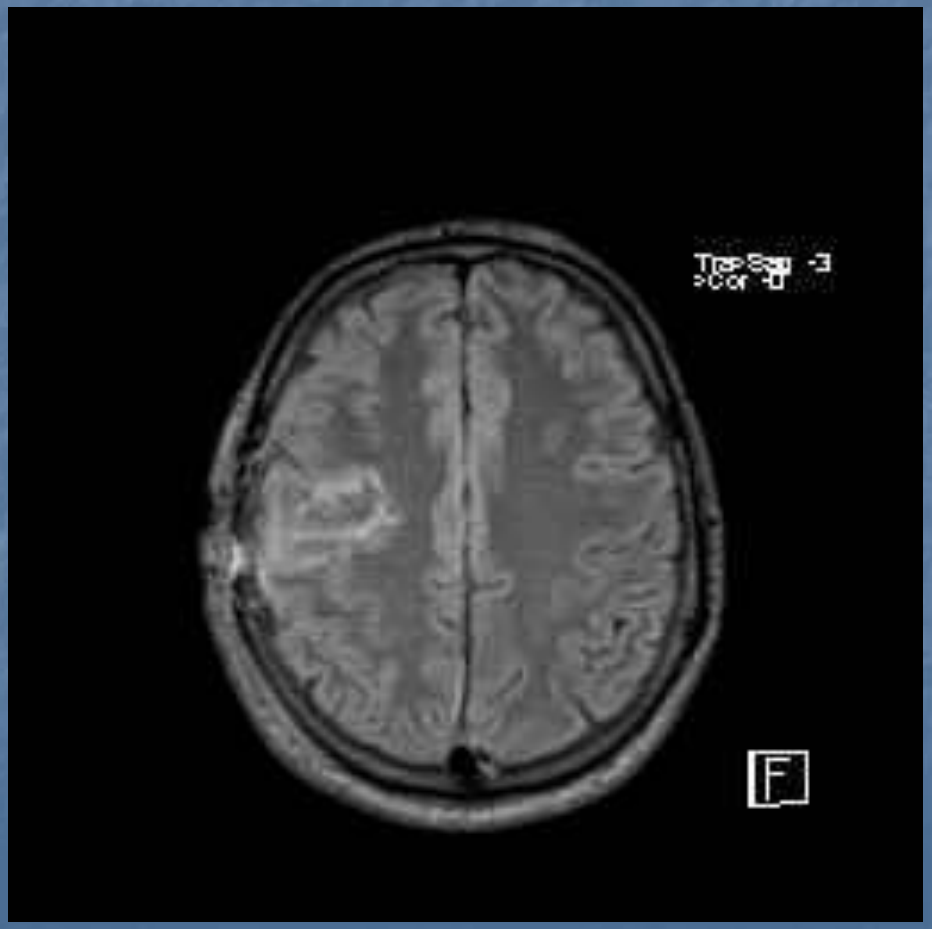
DIAGNOSI:

GLIOMA MALIGNO DIFFUSO CON ASPETTI IMMUNOMORFOLOGICI COMPLESSIVI MEGLIO CONSISTENTI CON ASTROCITOMA ANAPLASTICO

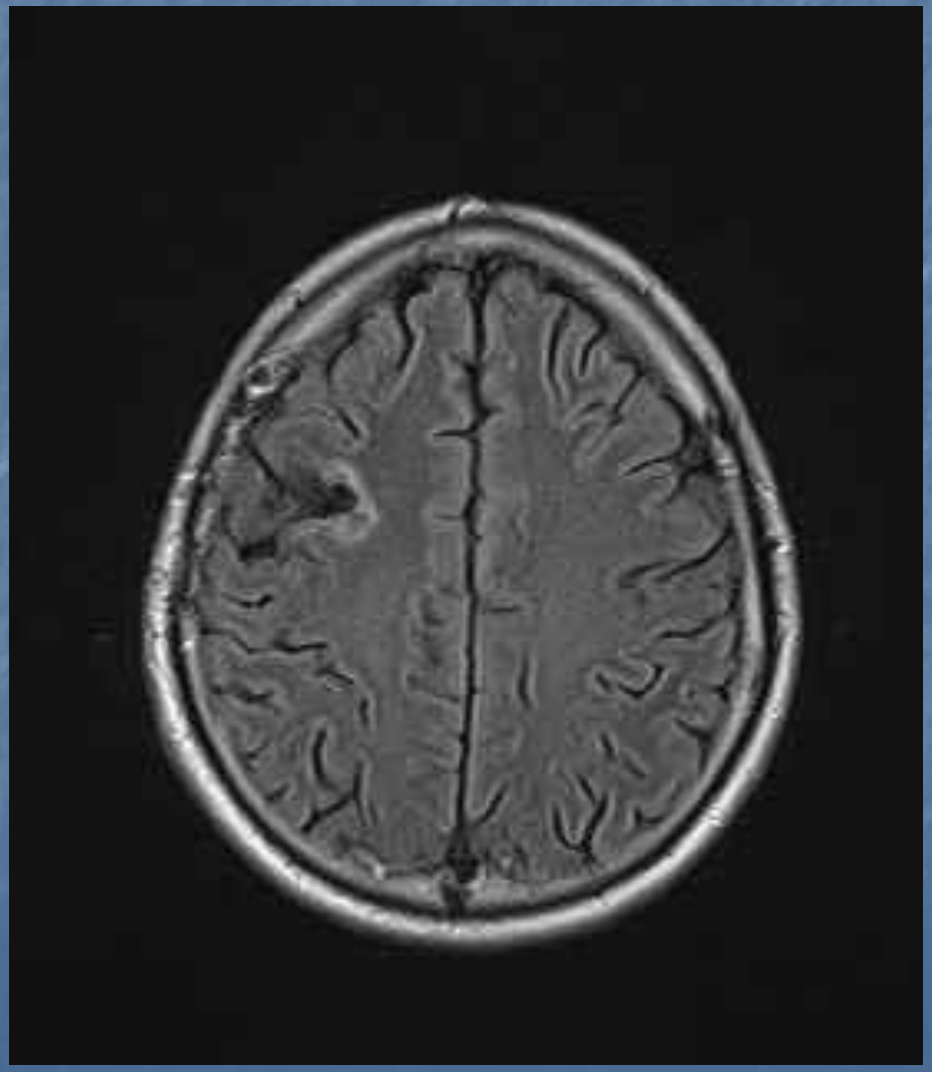
WHO: grado III. ICD-O code: 9401/3

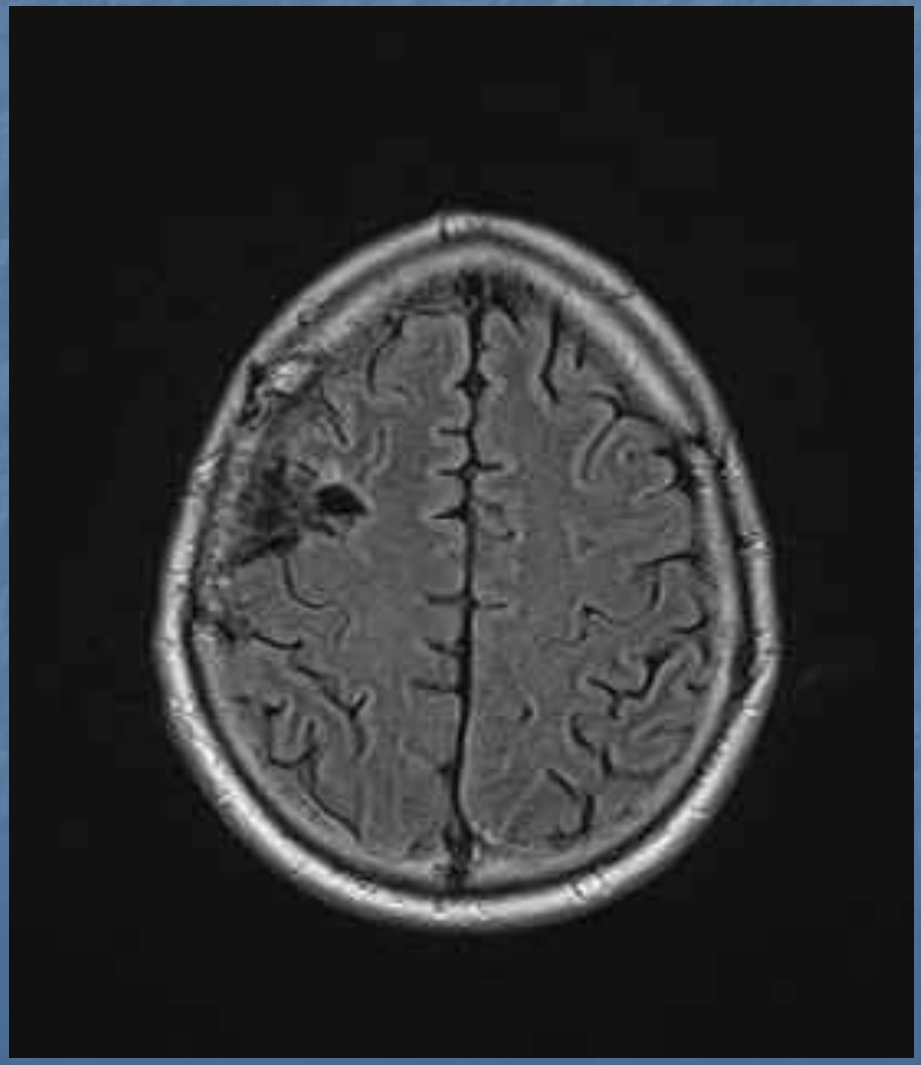
RM 24 ore dall'intervento



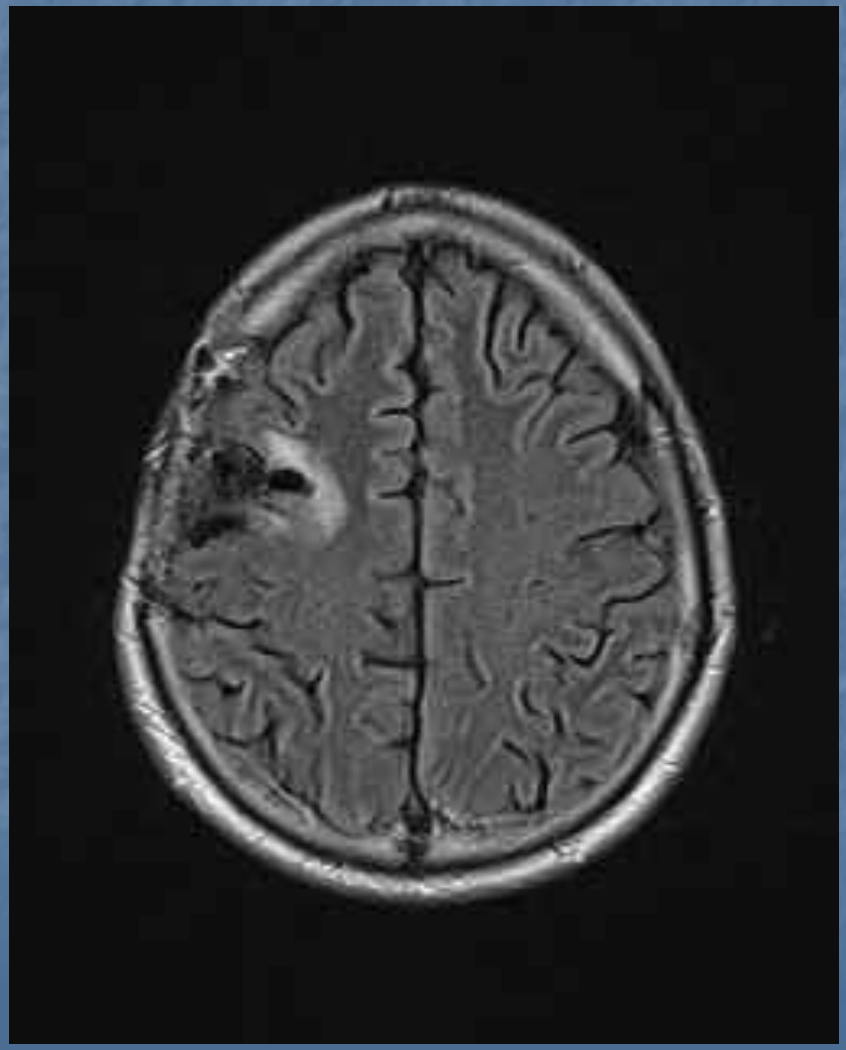


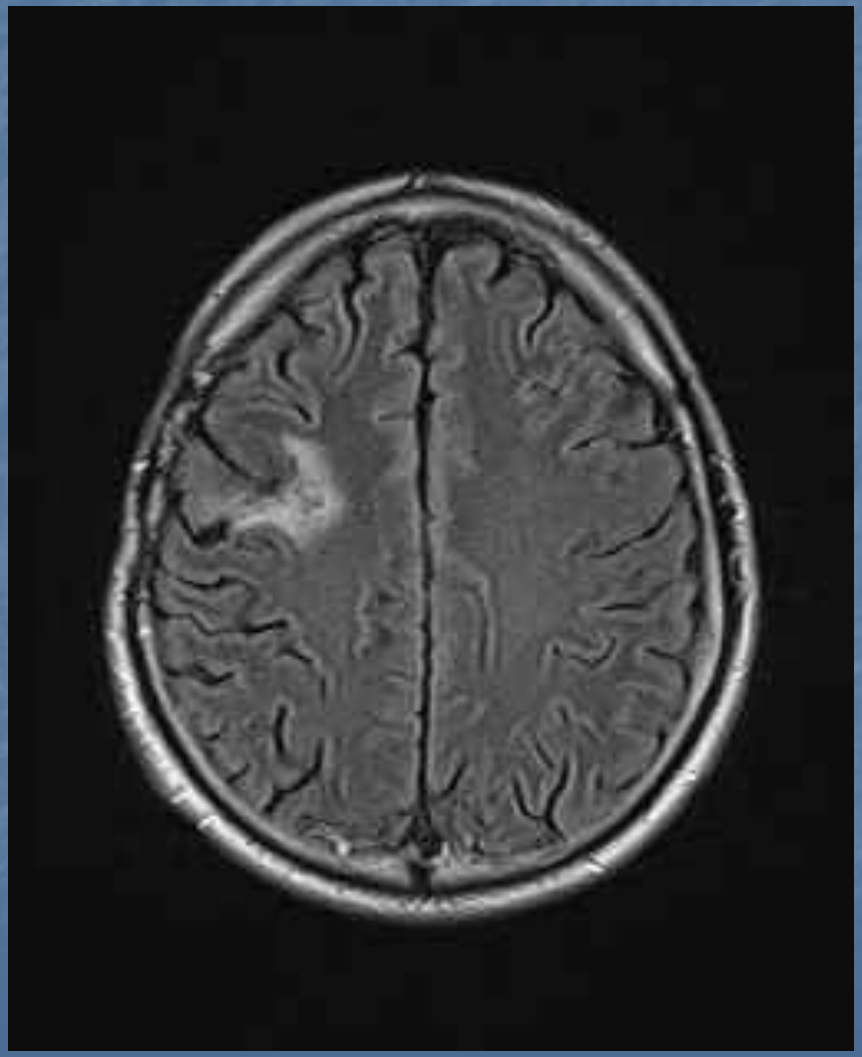
RM a 4 mesi dall'intervento



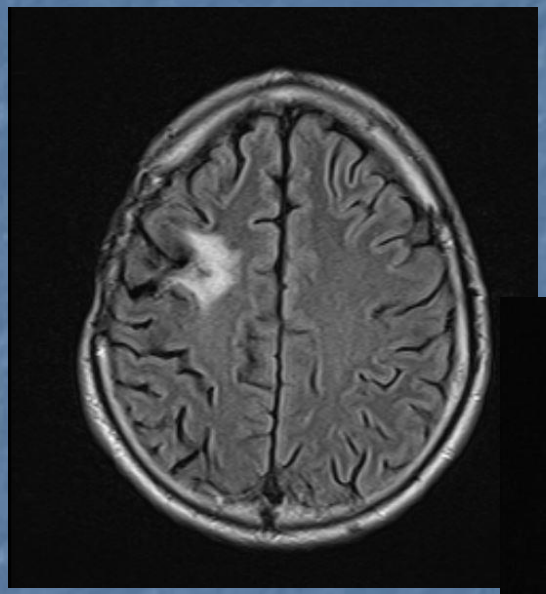


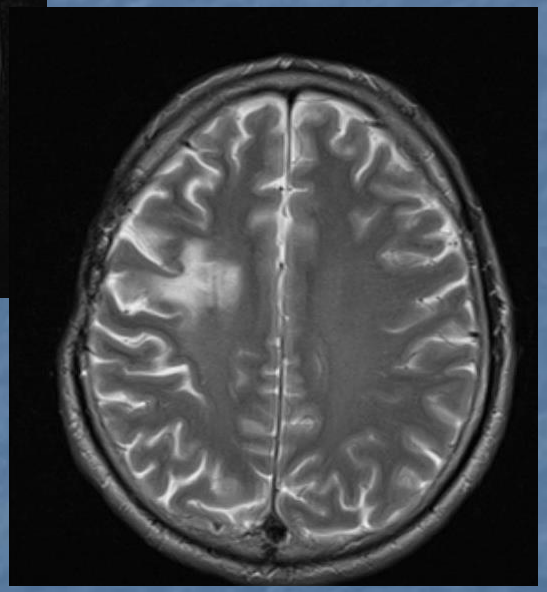
RM a 32 mesi dall'intervento

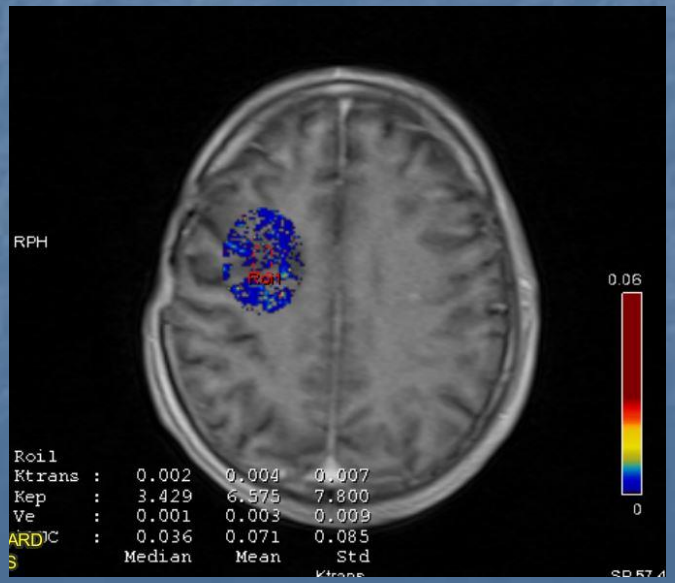


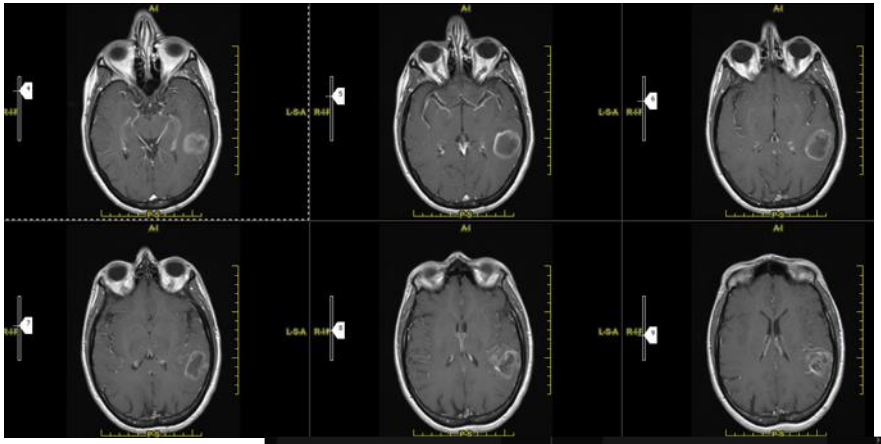


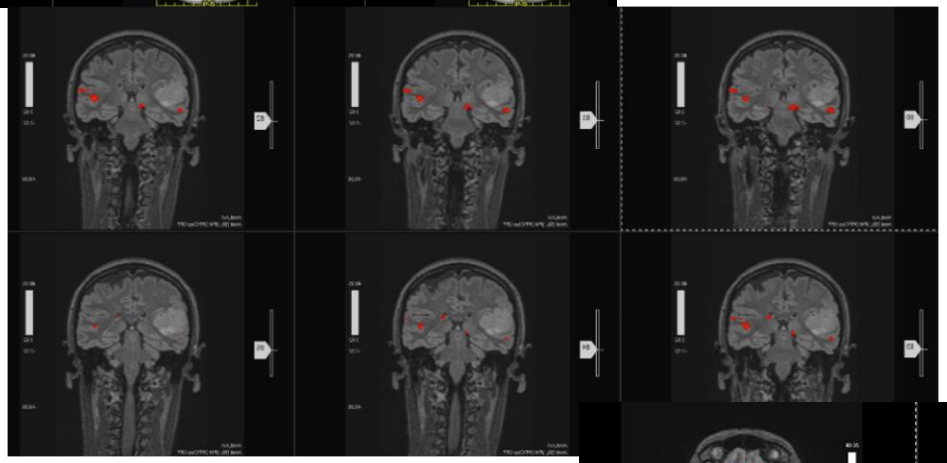
… 7 anni dopo l’intervento

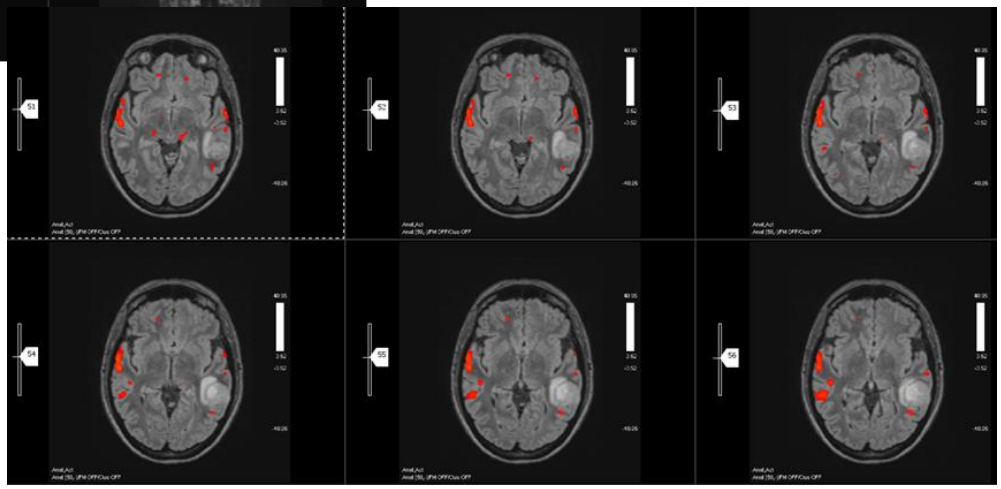






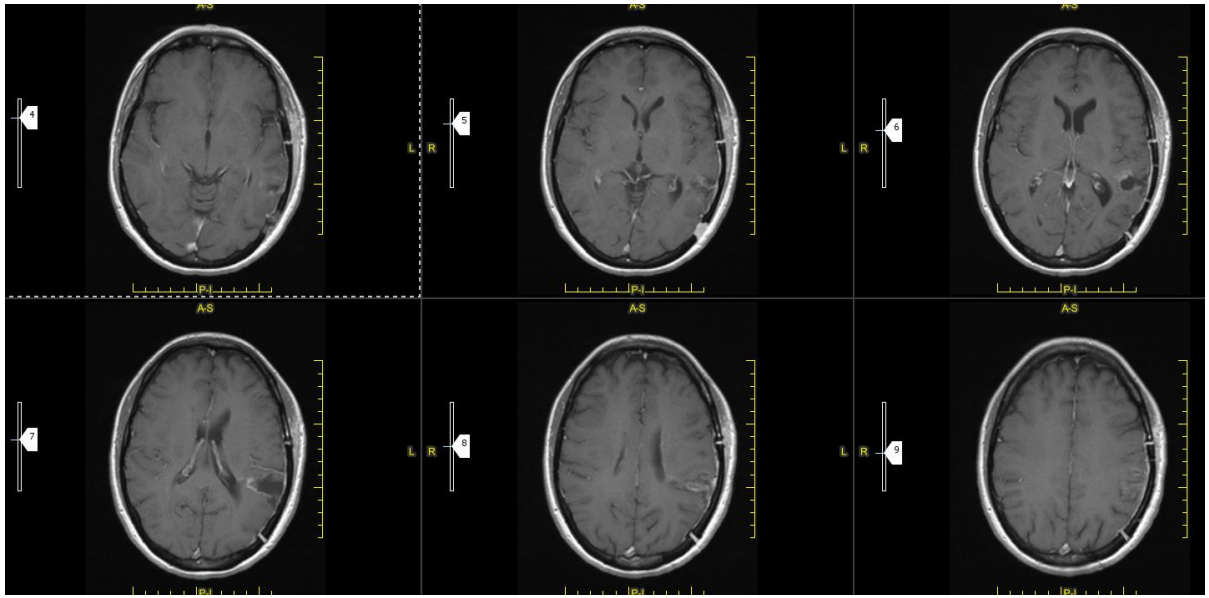


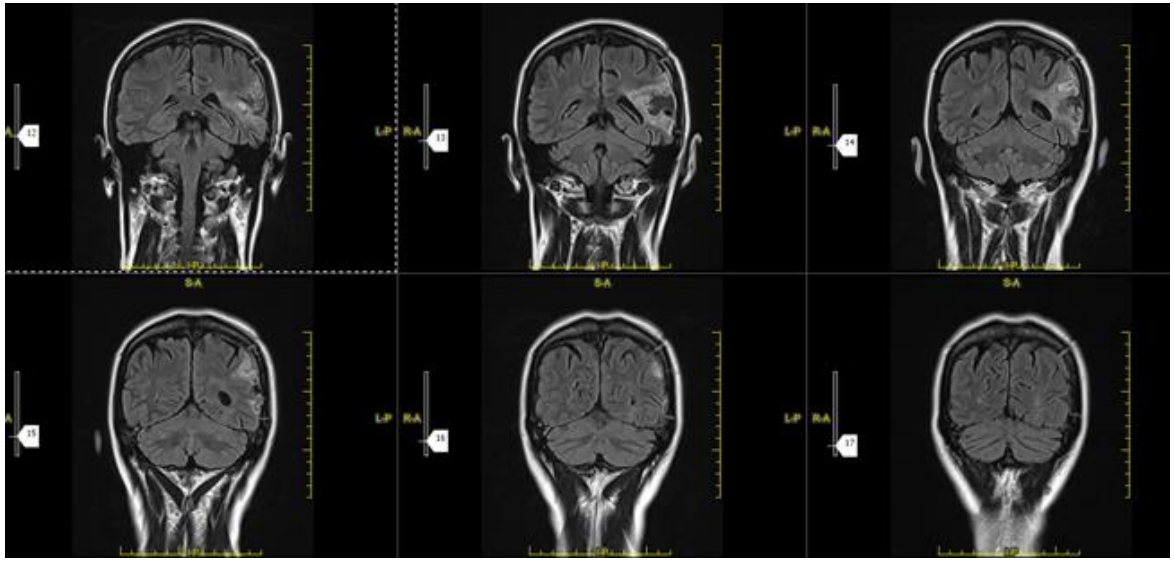




Donna, 45 aa
12/2014 disturbi fasici espressivi
Lesione opercolare sinistra
Glioma IDH1 IDH2 WT
LOH 1p/19q
Metilato 75%

RM immediatamente postoperatoria (09/02/15 24H)

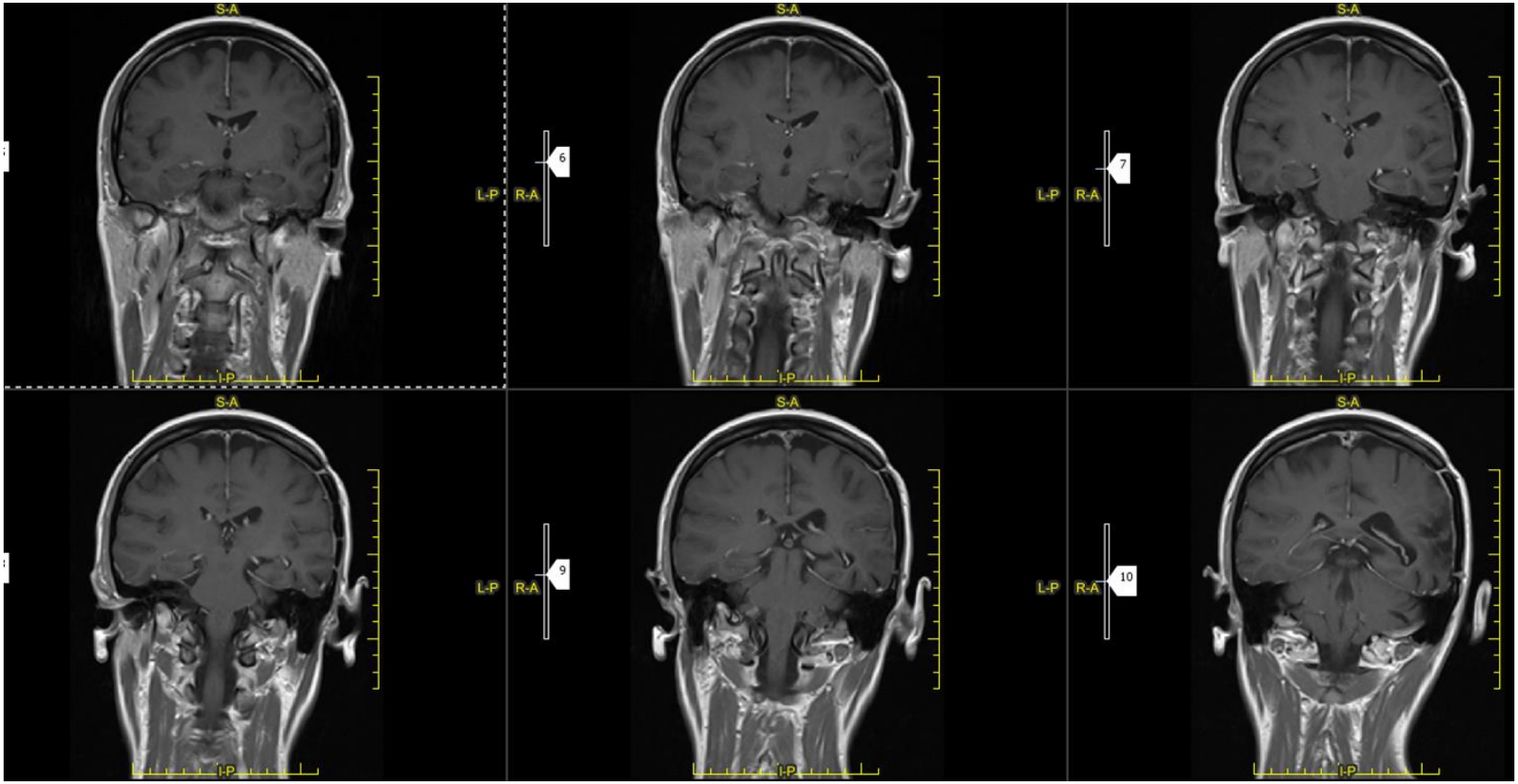




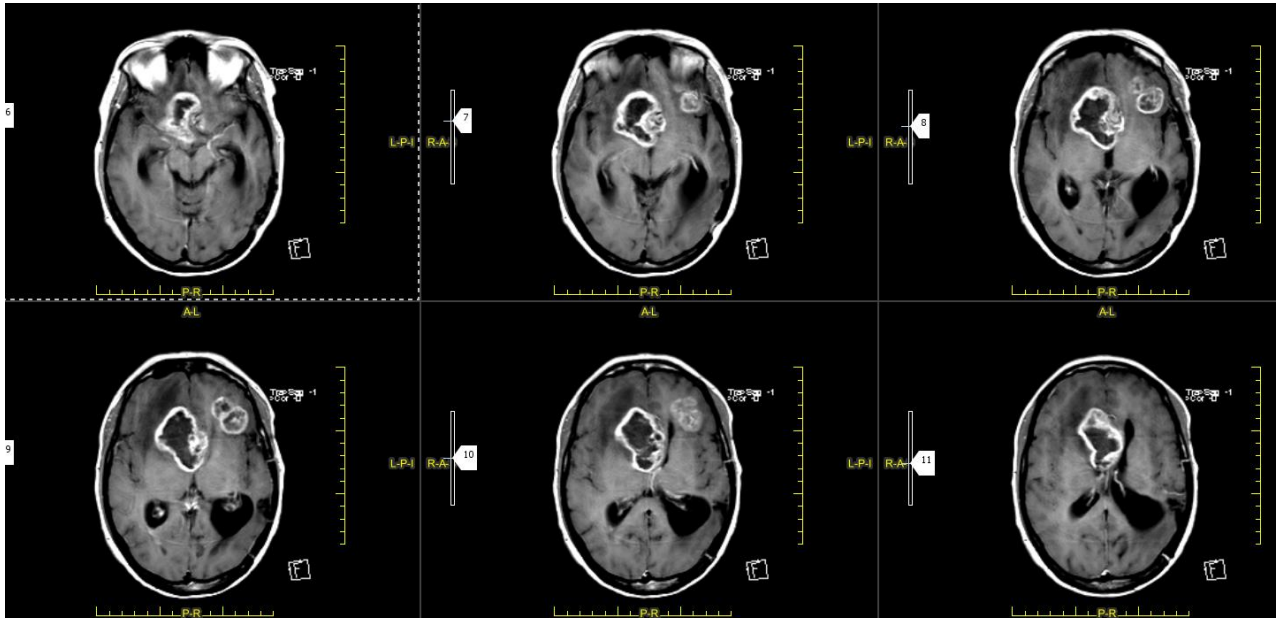
Eseguito protocollo STUPP.

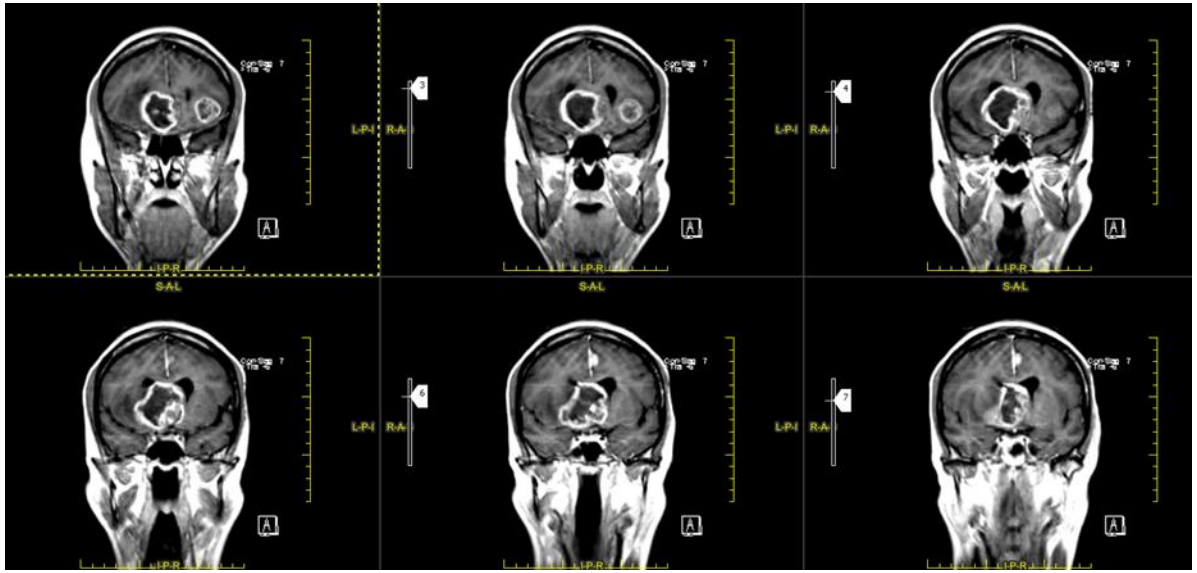
Follow up con stabilità di malattia fino al 2016.

RM encefalo del 20/06/2016:

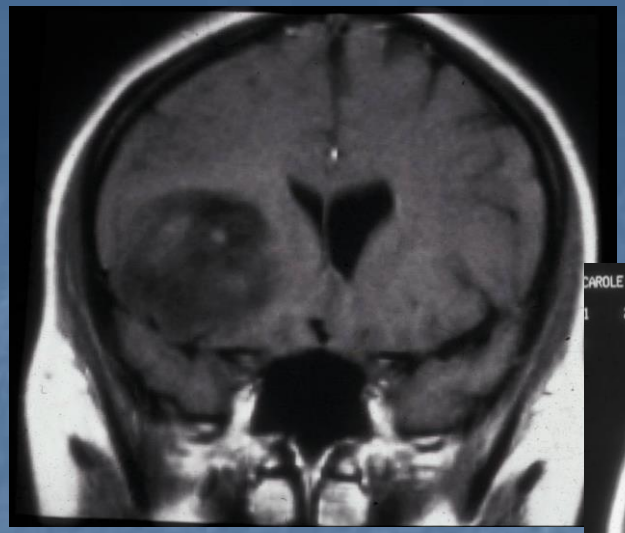


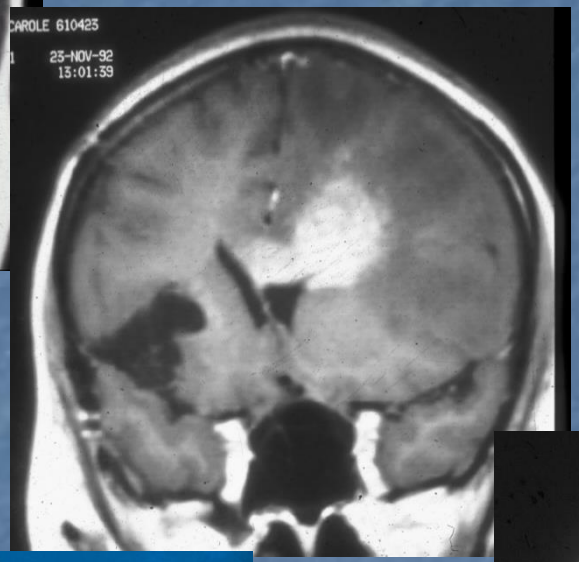
RM 11/10/2016:

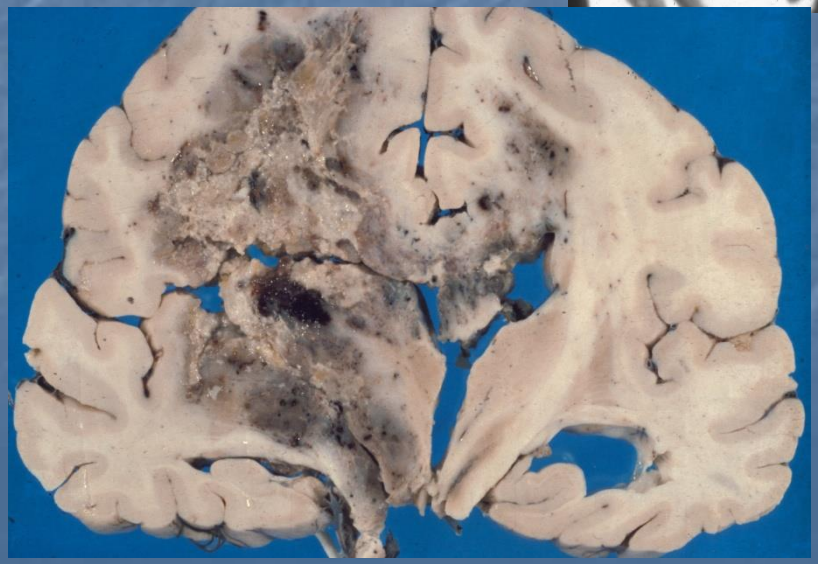


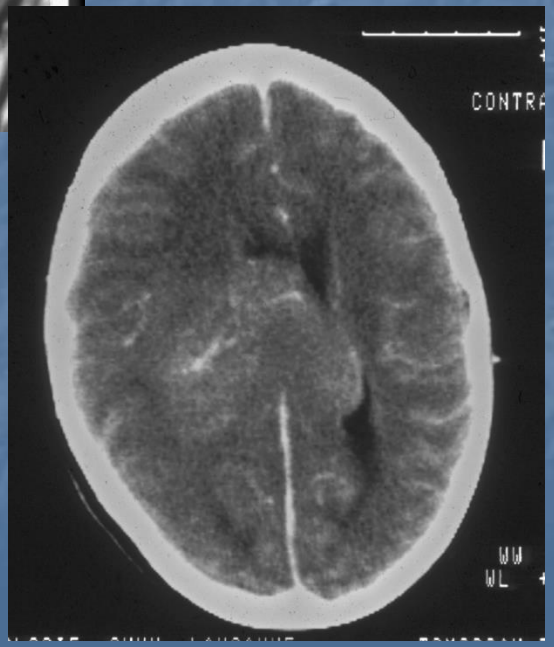


Malattia d’organo

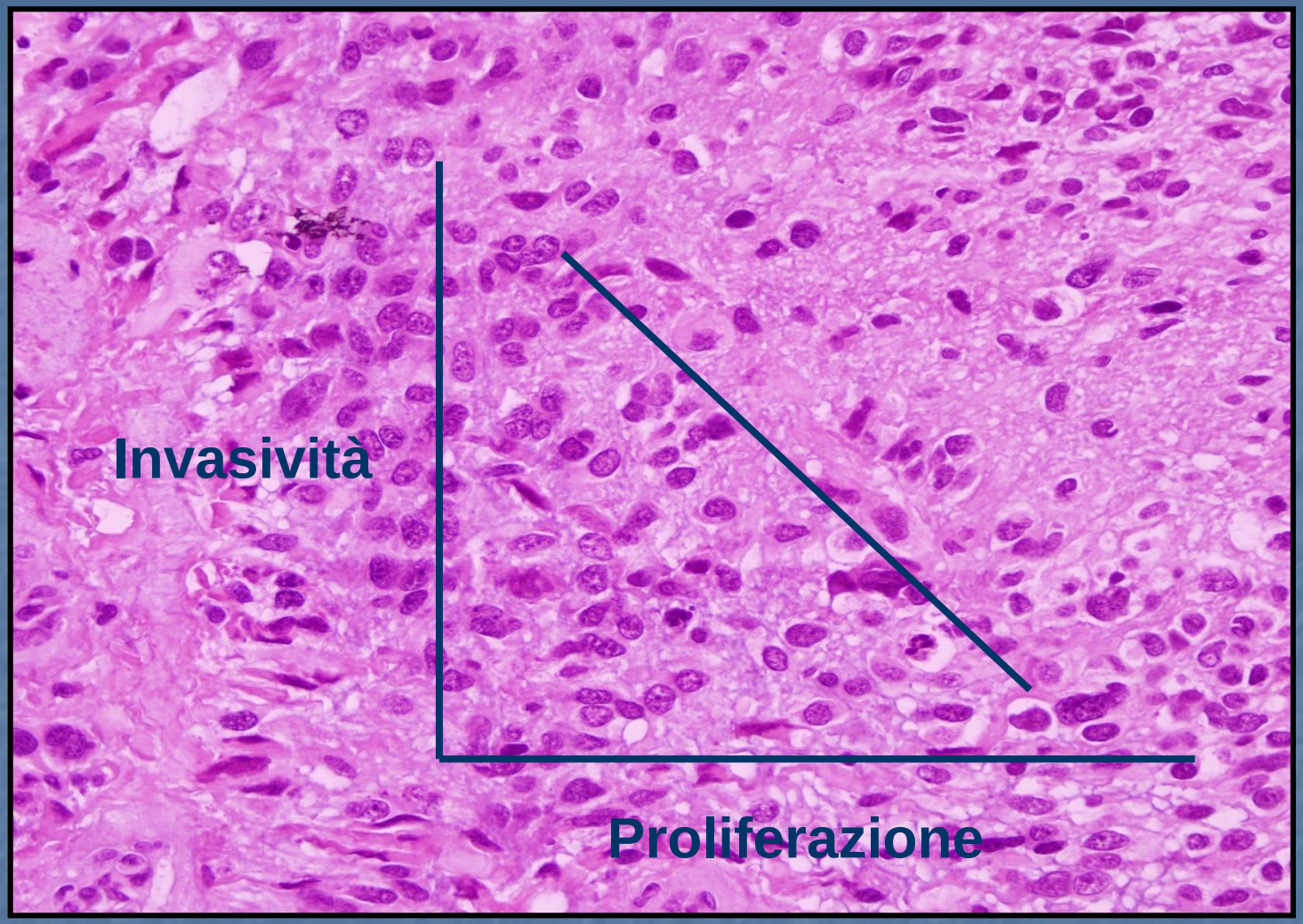








“Going and growing”



Mariani L et al., J Neurooncol, 2001

Kelly PJ, Daumas-Duport C et al, J Neurosurg, 1987

Scherer HJ, Brain, 1940

Ruolo della chirurgia

Chirurgia "diagnostica"

- **Biopsia stereotassica** ***(frame-guided o frameless)***

Chirurgia "terapeutica"

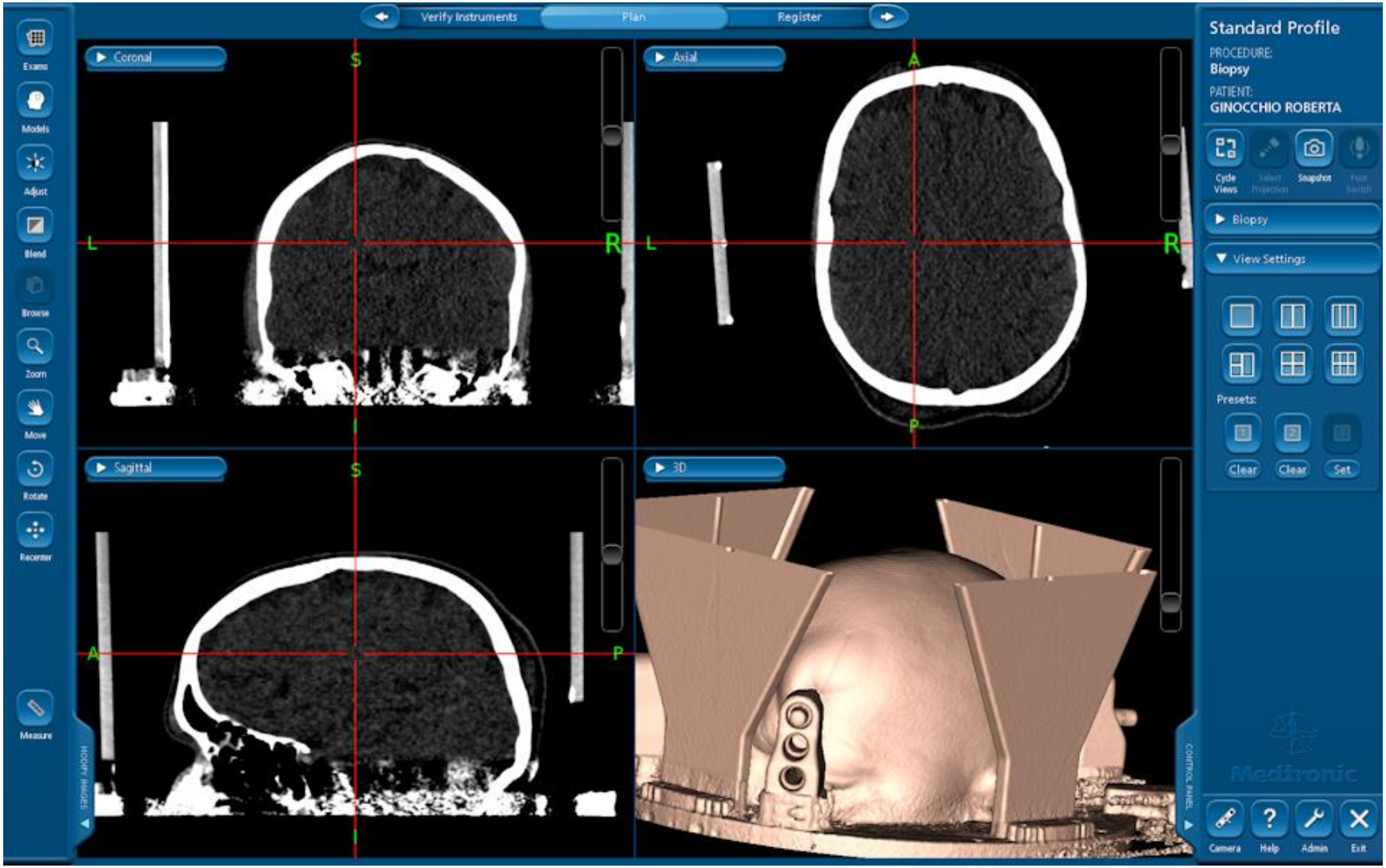
- **Chirurgia di exeresi**

Biopsia stereotassica

- Aumentare la sensibilità diagnostica! Come??
  - Selezione del target
    - *Fusione dell'imaging morfologico e metabolico*
  - Aumentare la quantità del campione da esaminare

Donna, 47 anni.
Marzo 2017 impaccio motorio all'emilato destro ed afasia transitoria.
Eseguiva TC ed RM (alterazione di segnale in sede frontale superiore sinistra in assenza di evidenti captazioni di contrasto in prima ipotesi compatibile con lesione proliferativa della linea gliale di basso grado).
Eseguiva quindi PET encefalo con F-dopa che mostrava la presenza di una chiara area di ipercaptazione di tracciante.

Diagnosi: Astrocitoma diffuso
IDH 1 WT – IDH 2 mutato
Metilato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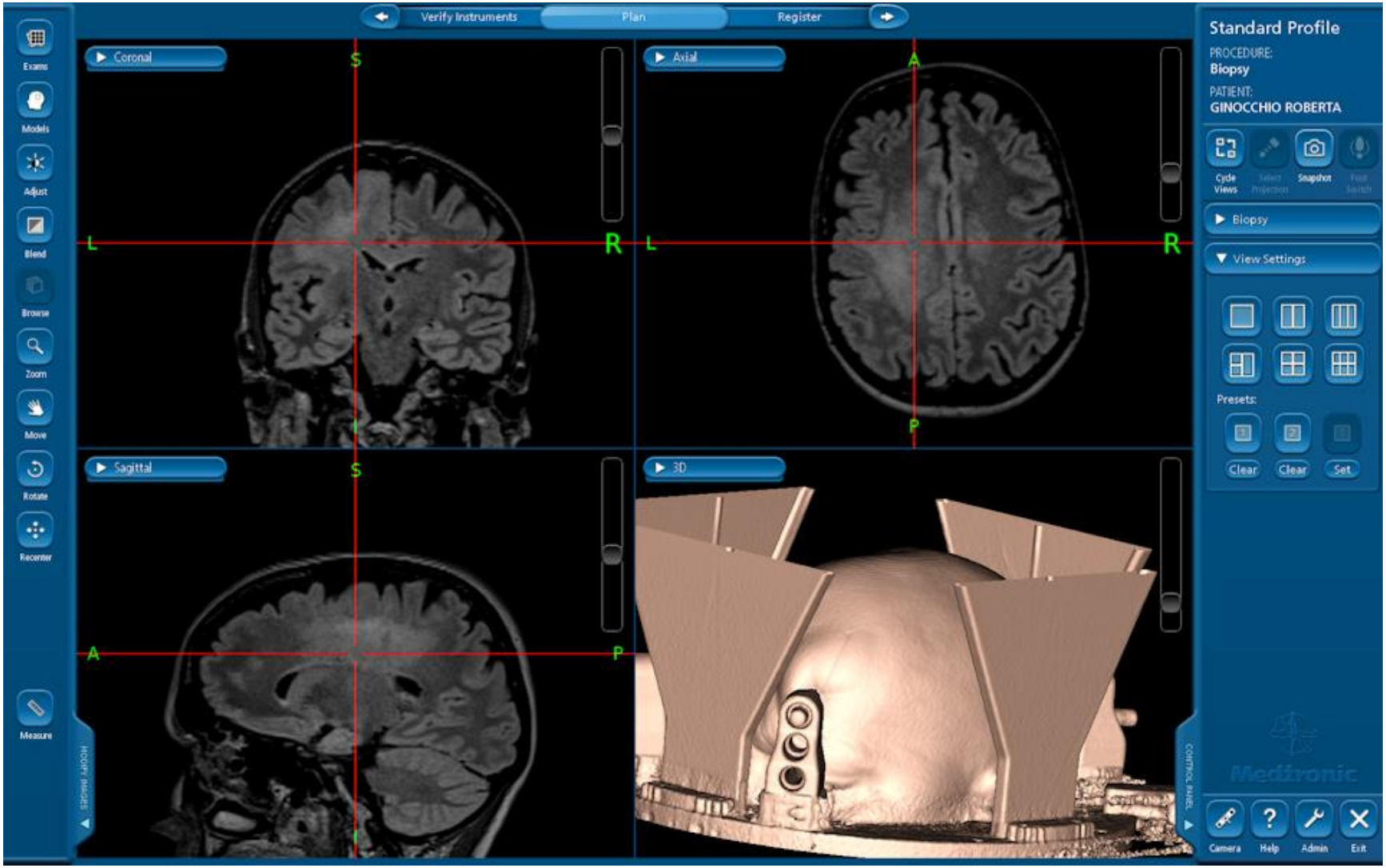
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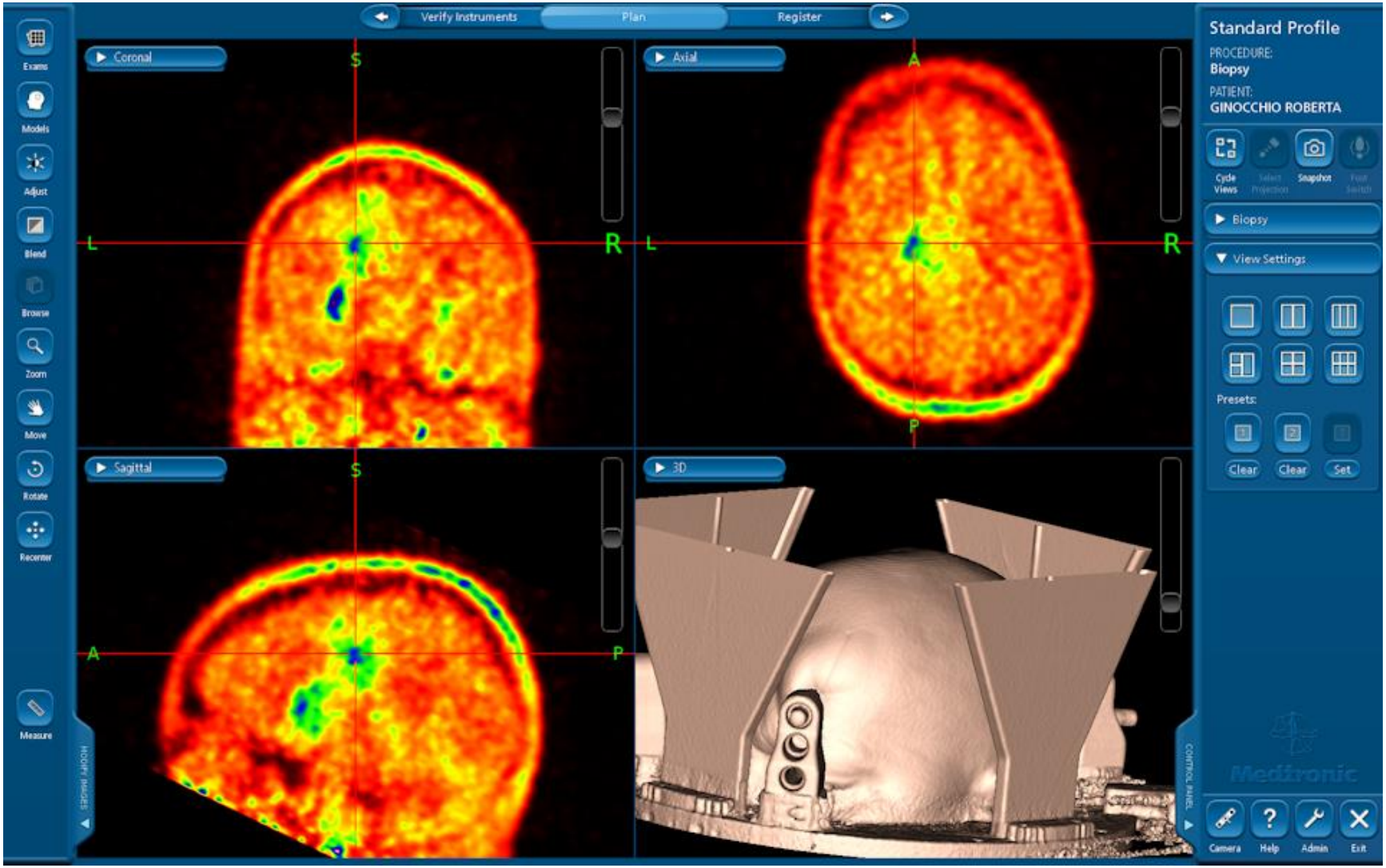
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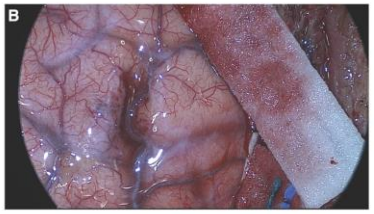
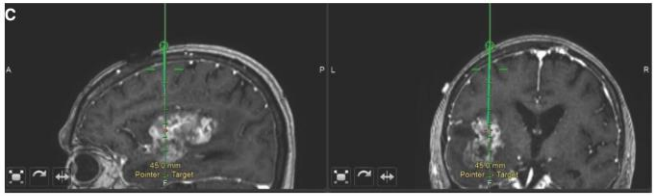
Journal of Neuro-Oncology
https://doi.org/10.1007/s11060-018-03014-w

CLINICAL STUDY

Tubular brain tumor biopsy to improves diagnostic yield for subcortical lesions

Evan D. Bander[1] · Samuel H. Jones[1] · David Pisapia[2] · Rajiv Magge[3] · Howard Fine[3] · Theodore H. Schwartz[1,4,5] · Rohan Ramakrishna[1]





	Stereotactic biopsy (n = 146) Mean (SD) or Freq (%)	Transtubular biopsy (n = 18) Mean (SD) or Freq (%)	p-value*
Biopsy/pathology outcomes			
Non-diagnostic sample obtained	19 (13.0%)	0 (0%)	0.1346
Frozen section obtained	119 (82.1%)	18 (100%)	0.0457
Frozen section volume	0.07 (0.1)	0.10 (0.1)	0.061
Permanent section obtained	139 (95.2%)	18 (100%)	1.0000
Permanent section volume (cm^3)	0.3 (0.9)	1.26 (1.1)	**< 0.0001**
Patient outcomes			
Post-biopsy hemorrhage	3 (2.1%)	1 (5.6%)	0.3691
Post-biopsy infection	2 (1.4%)	0 (0%)	1.000
Re-operation necessary for diagnosis	6 (4.1%)	0 (0%)	1.000

Ruolo della chirurgia

Bias

- Eterogeneità e limitatezza dei campioni
- Classificazione
- Definizione dell’estensione della resezione
- Pianificazione e tecnica chirurgica
- Studi retrospettivi e non randomizzati (classe III)

Chirurgia d'exeresi

Indicazioni "tradizionali"

- **citoriduttivo** ***(decompressivo e propedeutico alla terapia adiuvante)***
- **diagnostico** ***(tipo e grading istologico)***
- **ricerca "di base"** ***(terapia traslazionale)***

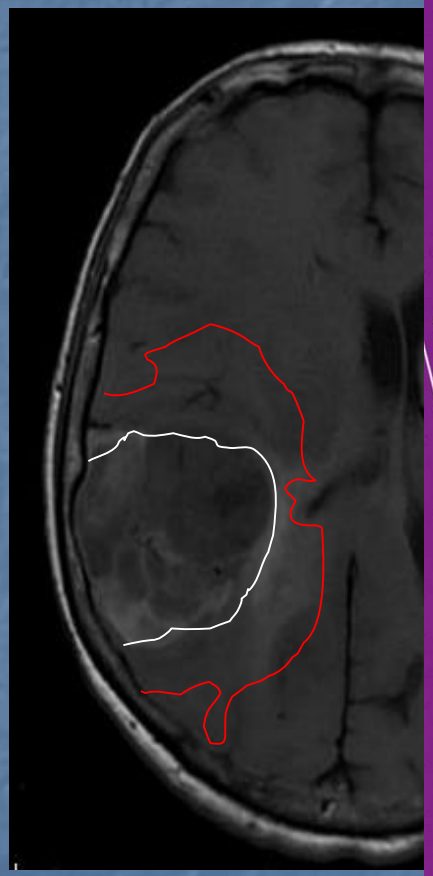
Problematiche "aperte"

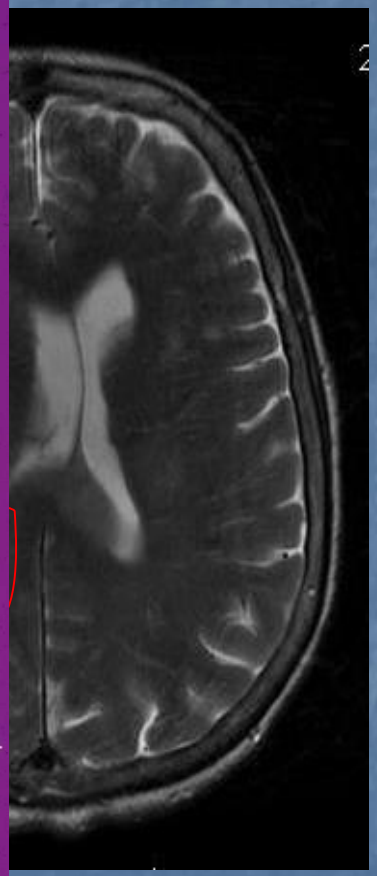
- **significatività del volume tumorale residuo post-chirurgico**
- **indicazioni chirurgiche in progressione di malattia**

Implicazioni "future"

- **neuroncologia locale** **(targeting molecolare)**

Target “chirurgico” vs Target “biologico”





CORRELAZIONE TRA PERCENTUALE DI RESEZIONE E SOPRAVVIVENZA

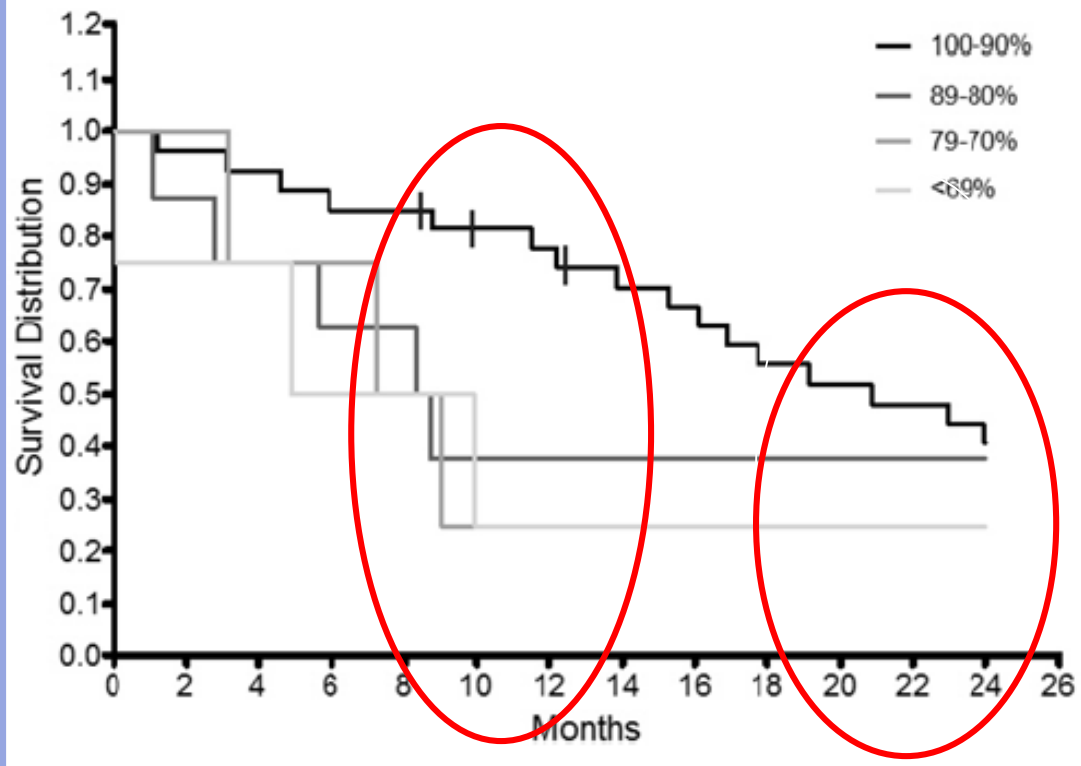


FIG. 1. Kaplan-Meier survival curve representing patients who underwent craniotomy for glioblastoma stratified by EOR. The EOR was associated with a significant difference in mortality at 1 year (p = 0.043), but not at 2 years (p = 0.350), among the 4 groups.

J Neurosurg 117:851–859, 2012

*DANIEL ORRINGER, M.D.,[1] DARRYL LAU, B.A.,[2] SAMEER KHATRI, B.S.,[2] GRETTEL J. ZAMORA-BERRIDI, M.H.S.,[2] KATHY ZHANG, B.A.,[2] CHRIS WU, B.S.,[2] NEERAJ CHAUDHARY, M.B.B.S., M.R.C.S., F.R.C.R.,[3] AND OREN SAGHER, M.D.[1]

Departments of [1]Neurosurgery and [3]Radiology, University of Michigan; and [2]University of Michigan Medical School, Ann Arbor, Michigan

CORRELAZIONE TRA PERCENTUALE DI RESEZIONE E SOPRAVVIVENZA

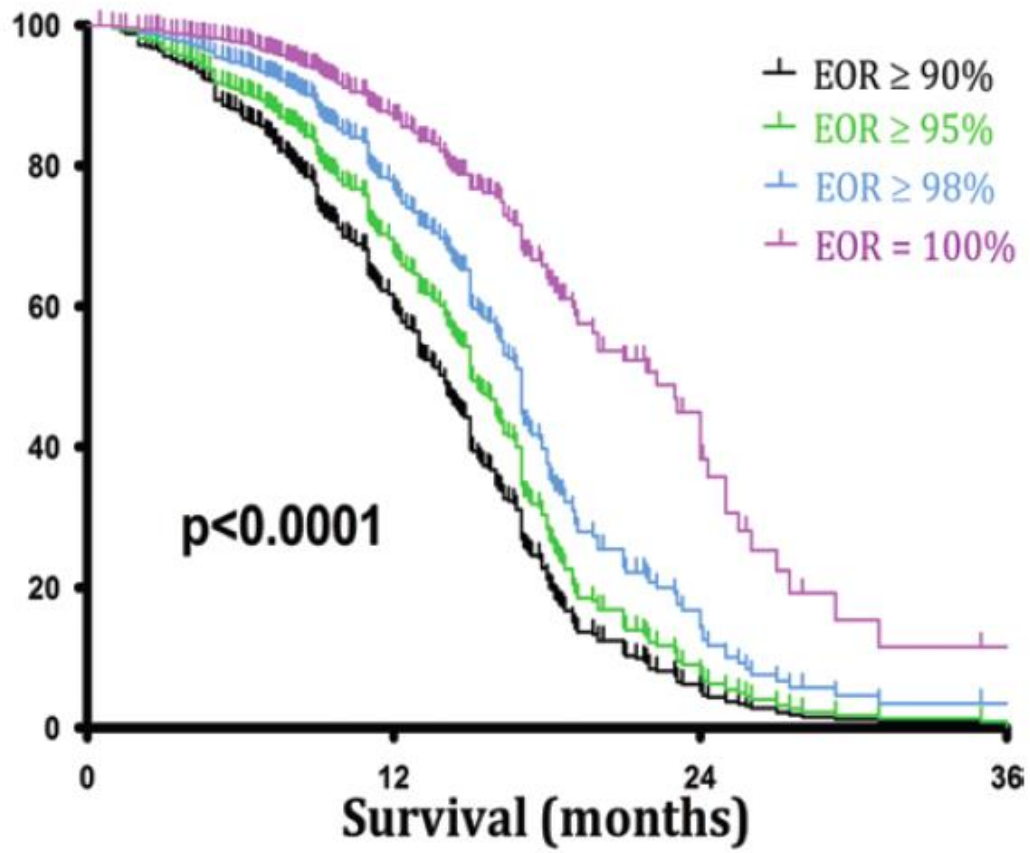


FIG. 4. Stepwise improvement in overall survival when comparing 90%, 95%, 98%, and 100% EOR thresholds.

J Neurosurg 115:3–8, 2011

NADER SANAI, M.D.,[1] MEI-YIN POLLEY, PH.D.,[2] MICHAEL W. MCDERMOTT, M.D.,[1] ANDREW T. PARSA, M.D., PH.D.,[1] AND MITCHEL S. BERGER, M.D.[1]

[1]Brain Tumor Research Center, and [2]Division of Biostatistics, Department of Neurological Surgery, University of California, San Francisco, California

CORRELAZIONE TRA PERCENTUALE DI RESEZIONE E SOPRAVVIVENZA

TABLE 1: Results of a multivariate Cox proportional hazards analysis to assess effect of EOR on survival in patients with GBM*

Variable	HR (95% CI)	p Value
age	1.01 (1.01–1.02)	<0.0001
KPS score	0.99 (0.98–0.99)	0.001
EOR	0.99 (0.98–0.99)	0.004
log (postop tumor vol +1)	1.07 (1.04–1.11)	<0.0001

* This final analysis designated age ($p < 0.0001$), KPS score ($p = 0.001$), EOR ($p = 0.004$), and postoperative tumor volume ($p < 0.0001$) as predictors of overall survival in patients with GBM.

Surgeon independant variable

Can be influeced by surgery

NADER SANAI, M.D.,[1] MEI-YIN POLLEY, PH.D.,[2] MICHAEL W. MCDERMOTT, M.D.,[1] ANDREW T. PARSA, M.D., PH.D.,[1] AND MITCHEL S. BERGER, M.D.[1]

[1]*Brain Tumor Research Center, and* [2]*Division of Biostatistics, Department of Neurological Surgery, University of California, San Francisco, California*

J Neurosurg 115:3–8, 2011

LA % DI RESEZIONE INFLUENZA LA SOPRAVVIVEZA

Criticità:

Valutazione del chirurgo e possibilità di resezione

La sede del tumore influenza sicuramente l'estensione della resezione (EOR)

L'EOR dipende dalla capacità del chirurgo di giudicare la presenza di tumore residuo durante la chirurgia.

Generalmente l'abilità del chirurgo di giudicare la completezza della resezione è inaccurata
(sembra che vicino alle aree più 'pericolose' la sovrastima dell'EOR sia maggiore)

J Neurosurg 117:851–859, 2012

Extent of resection in patients with glioblastoma: limiting factors, perception of resectability, and effect on survival

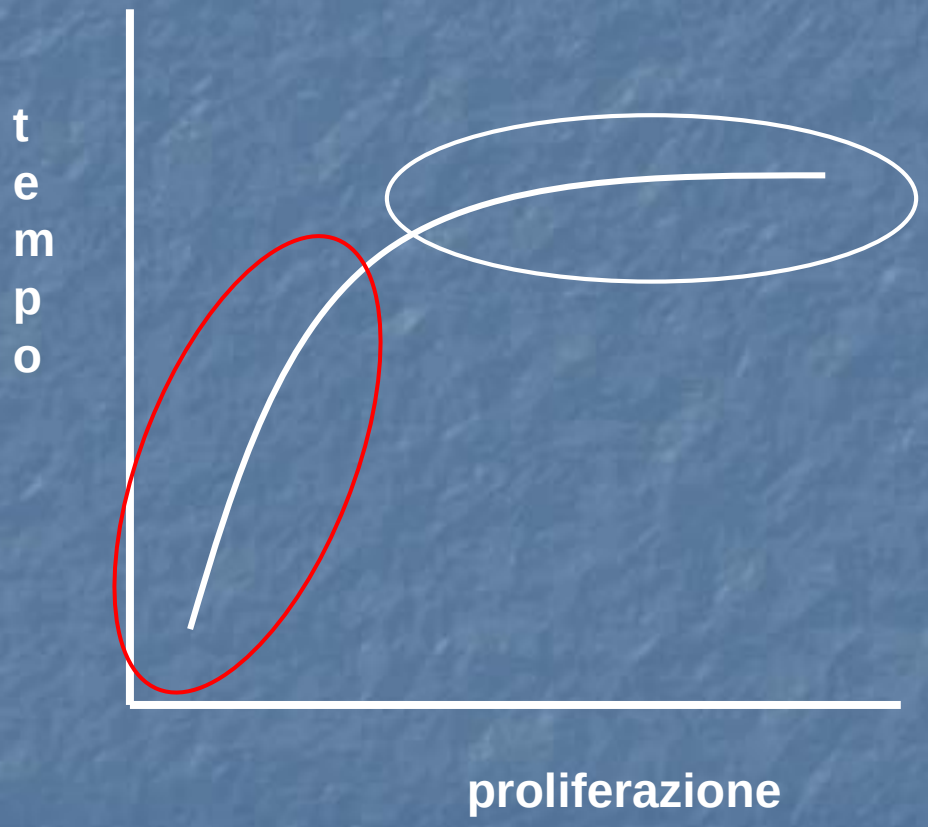
Clinical article

*Daniel Orringer, M.D.,[1] Darryl Lau, B.A.,[2] Sameer Khatri, B.S.,[2]
Grettel J. Zamora-Berridi, M.H.S.,[2] Kathy Zhang, B.A.,[2] Chris Wu, B.S.,[2]
Neeraj Chaudhary, M.B.B.S., M.R.C.S., F.R.C.R.,[3] and Oren Sagher, M.D.[1]

Departments of [1]Neurosurgery and [3]Radiology, University of Michigan; and [2]University of Michigan Medical School, Ann Arbor, Michigan

Ruolo della chirurgia

Citoriduzione



QUALI SONO LE SEDI CRITICHE

CORPO CALLOSO

Tanti gli articoli sulla via transcallosa
o sulla callosotomia per epilessia

J Neurosurg Pediatrics 7:98–103, 2011

Transcallosal interforniceal approach to pineal region tumors in 150 children

Clinical article

Wenqing Jia, M.D.,[1] Zhenyu Ma, M.D.,[1] Isabelle Yisha Liu, M.D.,[2] Yuqi Zhang, M.D.,[1] Ge Jia, M.D.,[1] and Weiqing Wan, M.D.[1]

[1]Department of Neurosurgery, TianTan Hospital, Capital University of Medical Science, Beijing, China; and [2]Washington University in St. Louis, School of Medicine, St. Louis, Missouri

Seizure 21 (2012) 307–309

Contents lists available at SciVerse ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Case report

Corpus callosotomy for treatment of pediatric refractory status epilepticus

Hansel M. Greiner[a,*], Jan-Mendelt Tillema[b], Barbara E. Hallinan[a], Katherine Holland[a], Ki-Hyeong Lee[c], Kerry R. Crone[d]

[a] Department of Pediatrics, Division of Child Neurology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH 45229, United States
[b] Department of Neurology, Division of Child Neurology, Mayo Clinic, Rochester, MN, United States
[c] Comprehensive Pediatric Epilepsy Center, Florida Hospital for Children, Orlando, FL, United States
[d] Division of Pediatric Neurosurgery, University of Cincinnati, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States

Ma pochi sulla chirurgia dei gliomi a livello del calloso

J Neurosurg 100:431–437, 2004

Surgical removal of corpus callosum infiltrated by low-grade glioma: functional outcome and oncological considerations

Hugues Duffau, M.D., Ph.D., Ihab Khalil, M.D., Peggy Gatignol, S.T., Dominique Denvil, M.D., and Laurent Capelle, M.D.

Departments of Neurosurgery and Neurology, Hôpital de la Salpêtrière, Paris, France

GANGLI DELLA BASE

Clinical Articles

Thalamic Astrocytomas: Surgical Anatomy and Results of a Pilot Series Using Maximum Microsurgical Removal

H.-J. Steiger, C. Götz, R. Schmid-Elsaesser, and **W. Stummer**

Department of Neurosurgery, Klinikum Grosshadern, Ludwig-Maximilians University Munich

Acta Neurochir (Wien) (2000) 142: 1327–1337

Age	Side	Tumor ∅	Histology	Approach and % removal	Postoperative complications	Events during follow-up	Follow-up time
4 ys	right	4.5 cm	pilocytic astrocytoma	transventricular 100%	–	–	52 months
6 ys	right	4 cm	anaplastic astrocytoma	infratentorial 80%	hydrocephalus, VP-shunt	–	16 months
25 ys	left	3.5 cm	astrocytoma II	transventricular 90%	partial hemianopia	–	10 months
54 ys	left	4 cm	glioblastoma	transventricular 70%	–	progression, death at 4 months	–
30 ys	right	5 cm	pilocytic astrocytoma	transventricular 90%	–	–	21 months
16 ys	left	3 cm	pilocytic astrocytoma	transventricular 100%	hydrocephalus, VP-shunt, transient disturbed consciousness	–	34 months
30 ys	left	5 cm	glioblastoma	transventricular 95%	partial hemianopia	–	6 months
48 ys	right	4 cm	anaplastic astrocytoma	transventricular 70%	–	progression, hydrocephalus, shunt	14 months
32 ys	right	3.5 cm	anaplastic astrocytoma	transventricular 70%	hydrocephalus, VP-shunt	progression	25 months
31 ys	right	2.5 cm	anaplastic astrocytoma	infratentorial 100%	hydrocephalus, VP-shunt	–	15 months
9 ys	left	5 cm	anaplastic astrocytoma	transventricular 95%	–	progression	16 months
64 ys	left	2 cm	anaplastic astrocytoma	infratentorial 100%	–	progression	10 months
10 ys	right	2 cm	anaplastic astrocytoma	infratentorial 100%	–	progression, hydrocephalus, death at 22 months	22 months
51 ys	right	5 cm	glioblastoma	transventricular 90%	–	–	10 months

INSULA

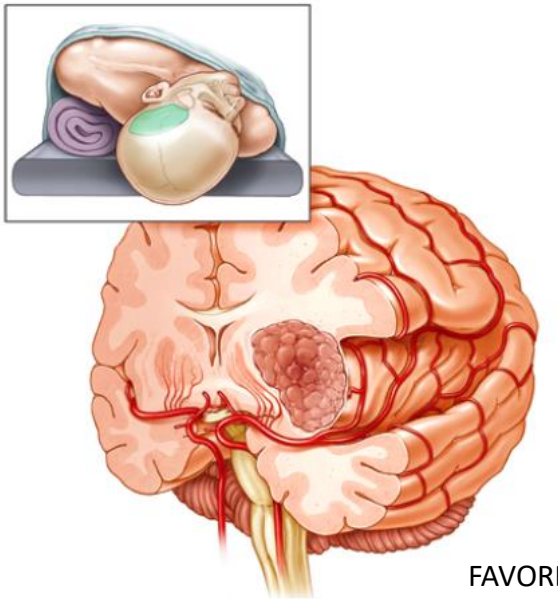
Resection of insular gliomas: the importance of lenticulostriate artery position

Clinical article

YARON A. MOSHEL, M.D., PH.D., JOSHUA D.S. MARCUS, B.A., ERIK C. PARKER, AND PATRICK J. KELLY, M.D.

Department of Neurosurgery, New York University School of Medicine, New York, New York

MENO FAVOREVOLE
PER RESEZIONE RADICALE



FAVOREVOLE

Insular gliomas: the case for surgical management

Clinical article

MATTHIAS SIMON, M.D.,[1] GEORG NEULOH, M.D.,[1] MAREC VON LEHE, M.D.,[1] BERNHARD MEYER, M.D.,[2] AND JOHANNES SCHRAMM, M.D.[1]

[1]Neurochirurgische Klinik, Universitätskliniken Bonn; and [2]Neurochirurgische Klinik, Technische Universität München, Klinikum rechts der Isar, München, Germany

J Neurosurg 110:685–695, 2009

A favore della chirurgia per i gradi I-III
Cautela nei pazienti con età > 60 anni e con GBM

AREA DEL LINGUAGGIO

Matthew J. McGirt, M.D.
Department of Neurosurgery,
The Neuro-Oncology Surgical
Outcomes Research Laboratory,
The Johns Hopkins University
School of Medicine,
Baltimore, Maryland

Debraj Mukherjee, M.D., M.P.H.
Department of Surgery,
The Neuro-Oncology Surgical
Outcomes Research Laboratory,
The Johns Hopkins University
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Baltimore, Maryland

Kaisorn L. Chaichana, M.D.
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Outcomes Research Laboratory,
The Johns Hopkins University
School of Medicine,
Baltimore, Maryland

Khoi D. Than, M.D.
Department of Neurosurgery,
University of Michigan School of Medicine,
Ann Arbor, Michigan

Jon D. Weingart, M.D.
Departments of Neurosurgery
and Oncology,
The Johns Hopkins University
School of Medicine,
Baltimore, Maryland

Alfredo Quinones-Hinojosa, M.D.

Association of Surgically Acquired Motor and Language Deficits on Overall Survival After Resection of Glioblastoma Multiforme

Lo sviluppo di nuovi deficit motori e del linguaggio nel postoperatorio
Si associava ad una <u>sopravvivenza ridotta</u> a parità di resezione e di
Trattamento, quindi non solo come già noto a ridotta qualità di vita!

Neurosurgery 65:463–470, 2009

AREA MOTORIA

Impact of Intraoperative Neurophysiological Monitoring on Surgery of High-Grade Gliomas

Theodoros Kombos, Thomas Picht, Athanasios Derdilopoulos, and Olaf Suess

J Clin Neurophysiol 2009; 26: 422-5

J Neurooncol (2010) 100:417–426
DOI 10.1007/s11060-010-0193-x

CLINICAL STUDY – PATIENT STUDY

Surgical treatment of high-grade gliomas in motor areas. The impact of different supportive technologies: a 171-patient series

Andrea Talacchi · Sergio Turazzi · Francesca Locatelli · Francesco Sala · Alberto Beltramello · Franco Alessandrini · Paolo Manganotti · Paola Lanteri · Roberta Gambin · Mario Ganau · Vincenzo Tramontano · Barbara Santini · Massimo Gerosa

FMRI CON NAVIGAZIONE + MONITORAGGIO NEUROFISIOLOGICO
Contribuiscono in modo significativo a migliorare l'EOR

TECNOLOGIE PER MIGLIORARE IL MARGINE DI RESEZIONE

PIANIFICAZIONE PREOPERATORIA e UTILIZZO DEL NEURONAVIGATORE

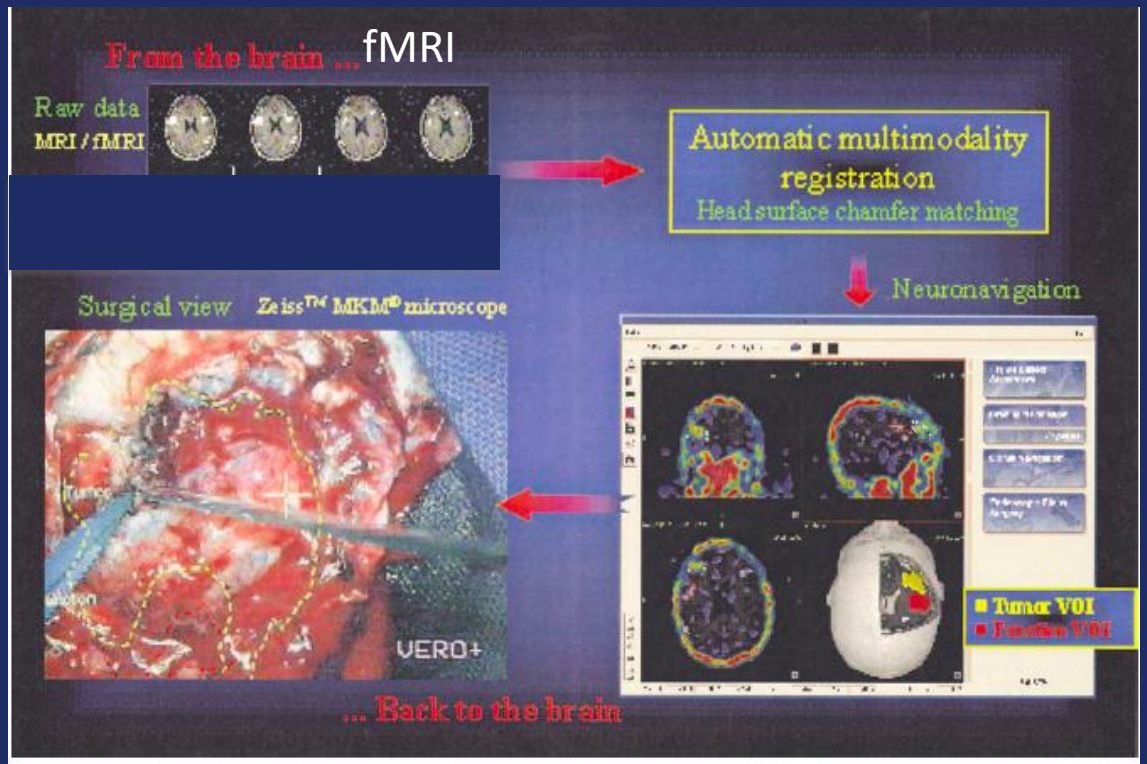
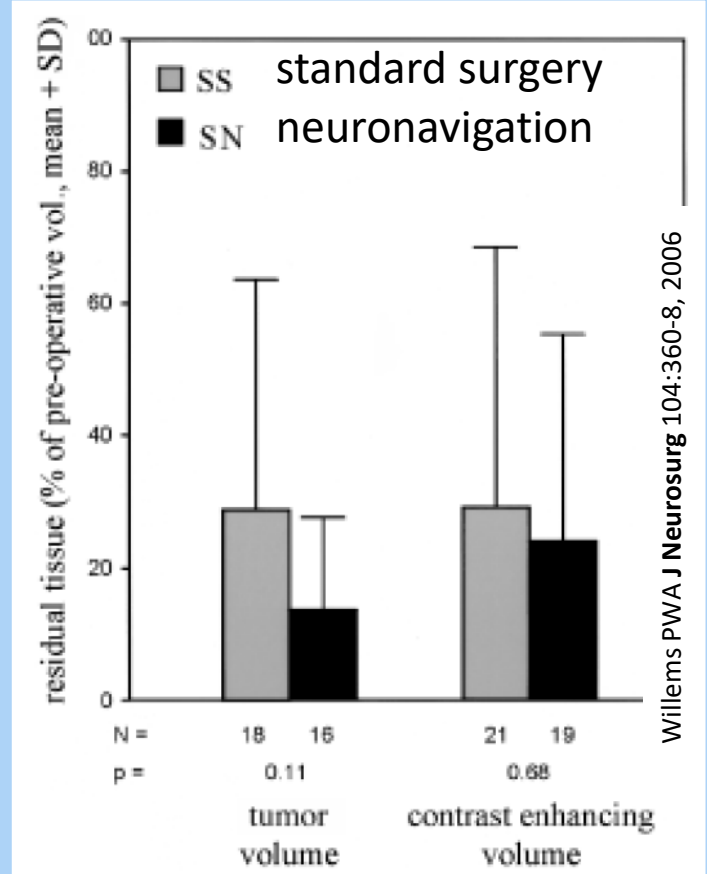
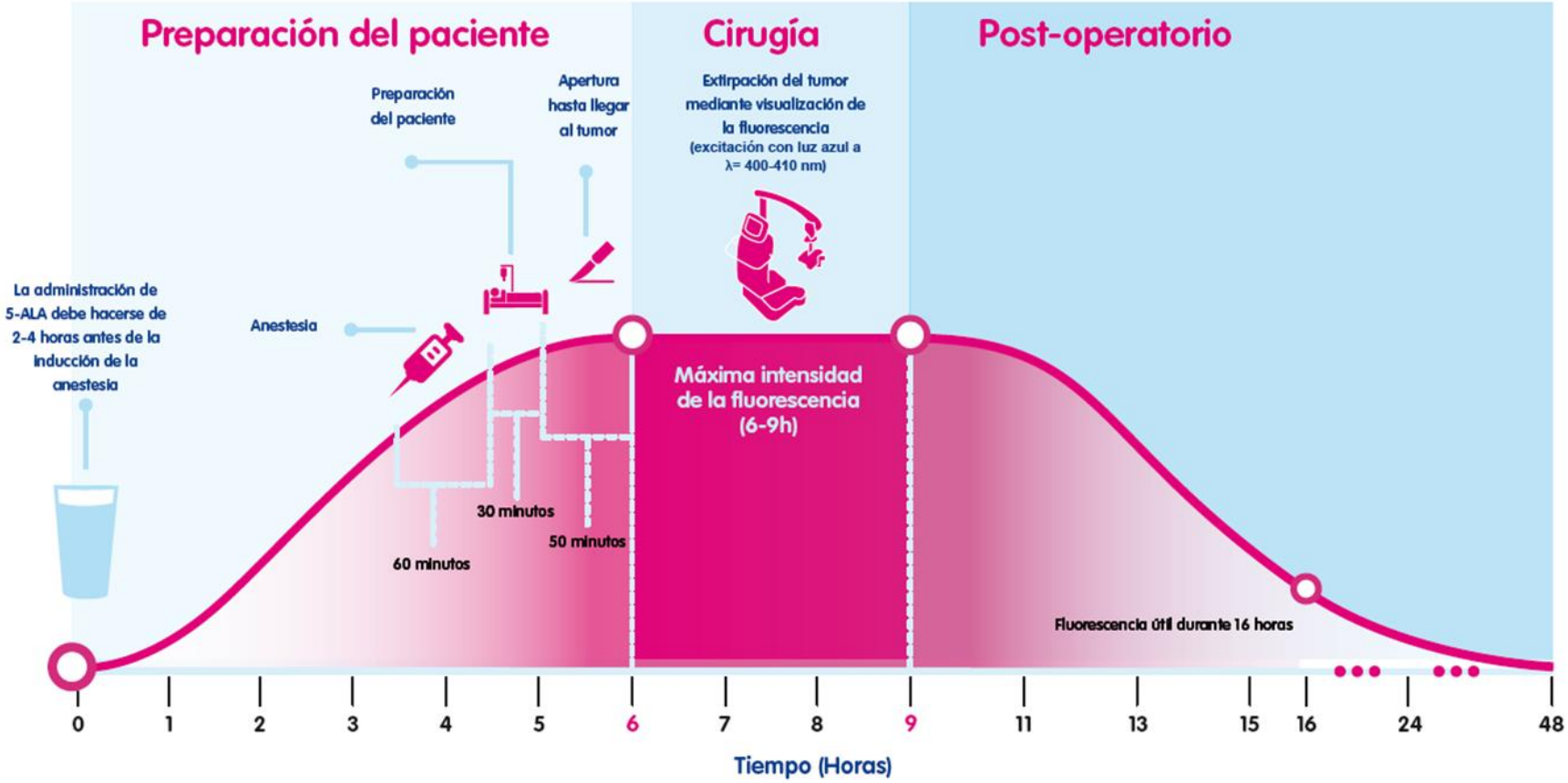


Fig. 3. Whole imaging and operative procedure: four steps done over 24 h (Patient 6). (1) Acquisition of the scintigraphic and anatomical and functional MR data on the morning of the first day. (2) Automatic registration of the images just after completion of the last examination. (3) Neuronavigation: planning of the operation scheduled for the afternoon; during this phase, the surgeon delineates manually the different VOIs around the tumor represented by the thallium fixation and the functional areas located around the tumor; he also determines the best surgical approach to the lesion. (4) Operation the next morning: the image of the microscope is registered with the anatomical MR data given by the external landmarks and the contours of the VOIs are projected into the microscope view along the direction of its optical axis.



Willems PWA **J Neurosurg** 104:360-8, 2006



Costi (circa 1000 Euro)
Fornitura del farmaco
«Patentino»
Preparazione (fotosensibilizzazione)

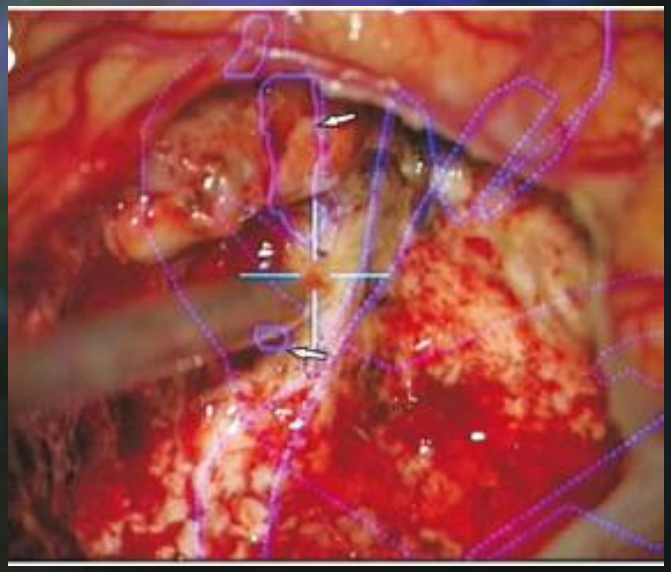
5- ALA

IL TESSUTO MALIGNO SINTETIZZA O ACCUMULA DELLE PROTEINE ENDOGENE FOTOSENSIBILIZZANTI DOPO LA SOMMINISTRAZIONE DI ACIDO 5-AMINOLEVULINICO IN ECCESSO.

SI TRATTA DI UN PRECURSORE NATURALE NELLA BIOSINTESI DELL'EME (PROTOPORFIRINA IX).

APPLICATO ANCHE SUI GLIOMI DALLA FINE ANNI'90.

Stummer W et al. **Neurosurgery** 1998; 42(3) 518-26

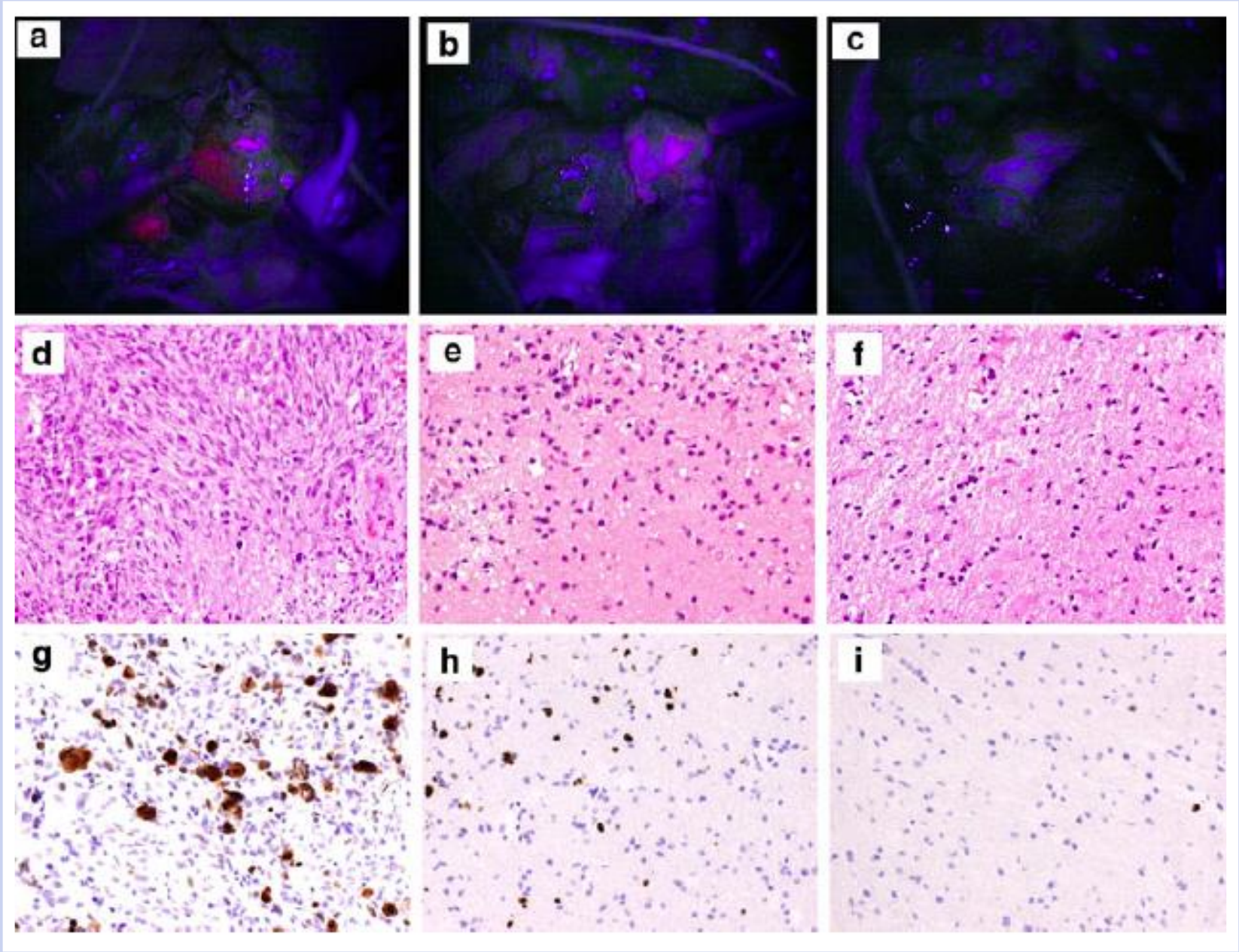


Eyuepoglu IY et al. PLOS one 2012; 7 (9) e44885

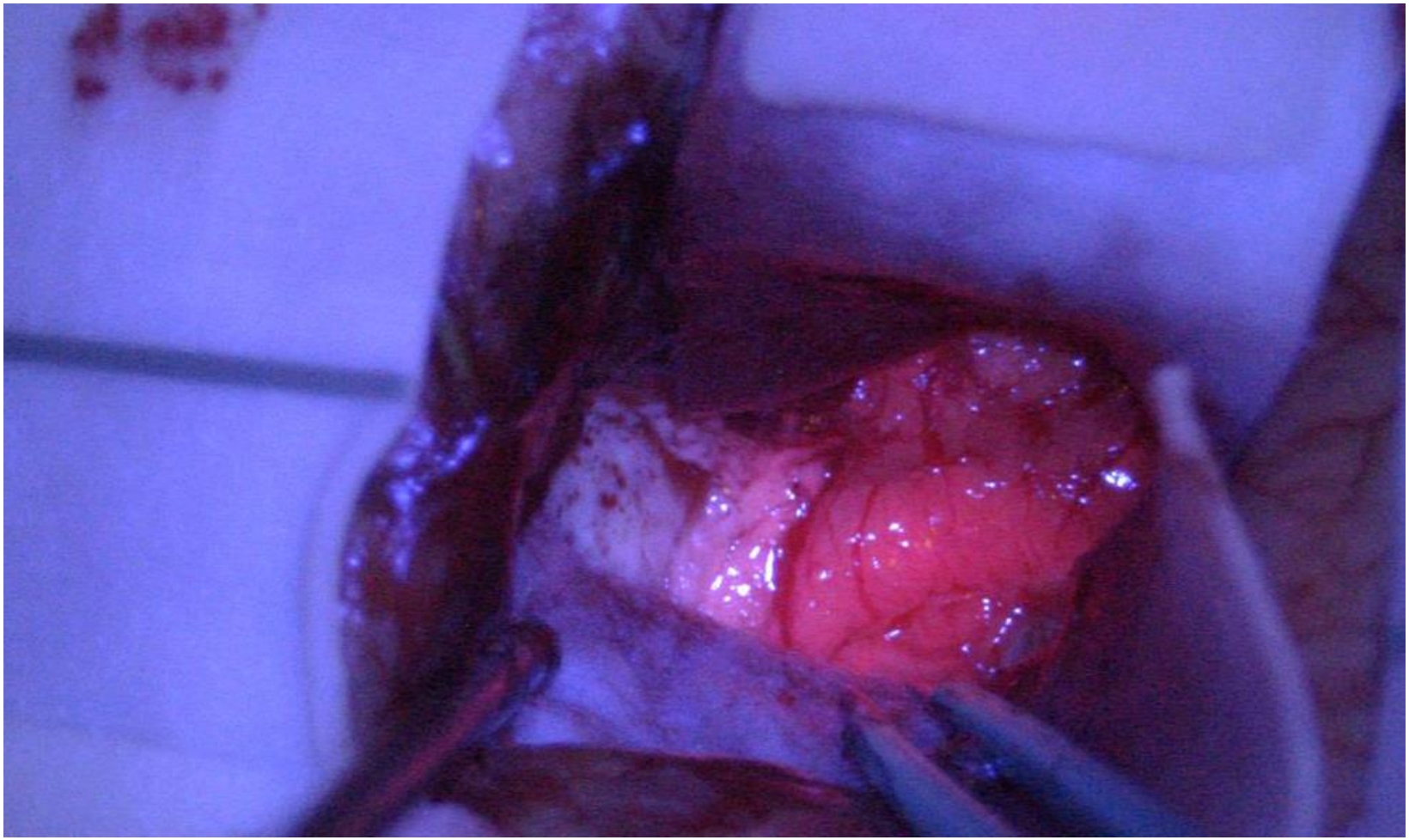
5-ALA intraop

H&E istologia

Ki-67



Diez Valle R et al. **J Neurooncol** 2011; 102: 105-13



Quando fermarsi ?
…coupling con IOM !!!

RMN Intraoperatoria (e DTI) e MEP – IntraOperative UltraSound (IOUS) – Contrast Enhanced UltraSound (CEUS)

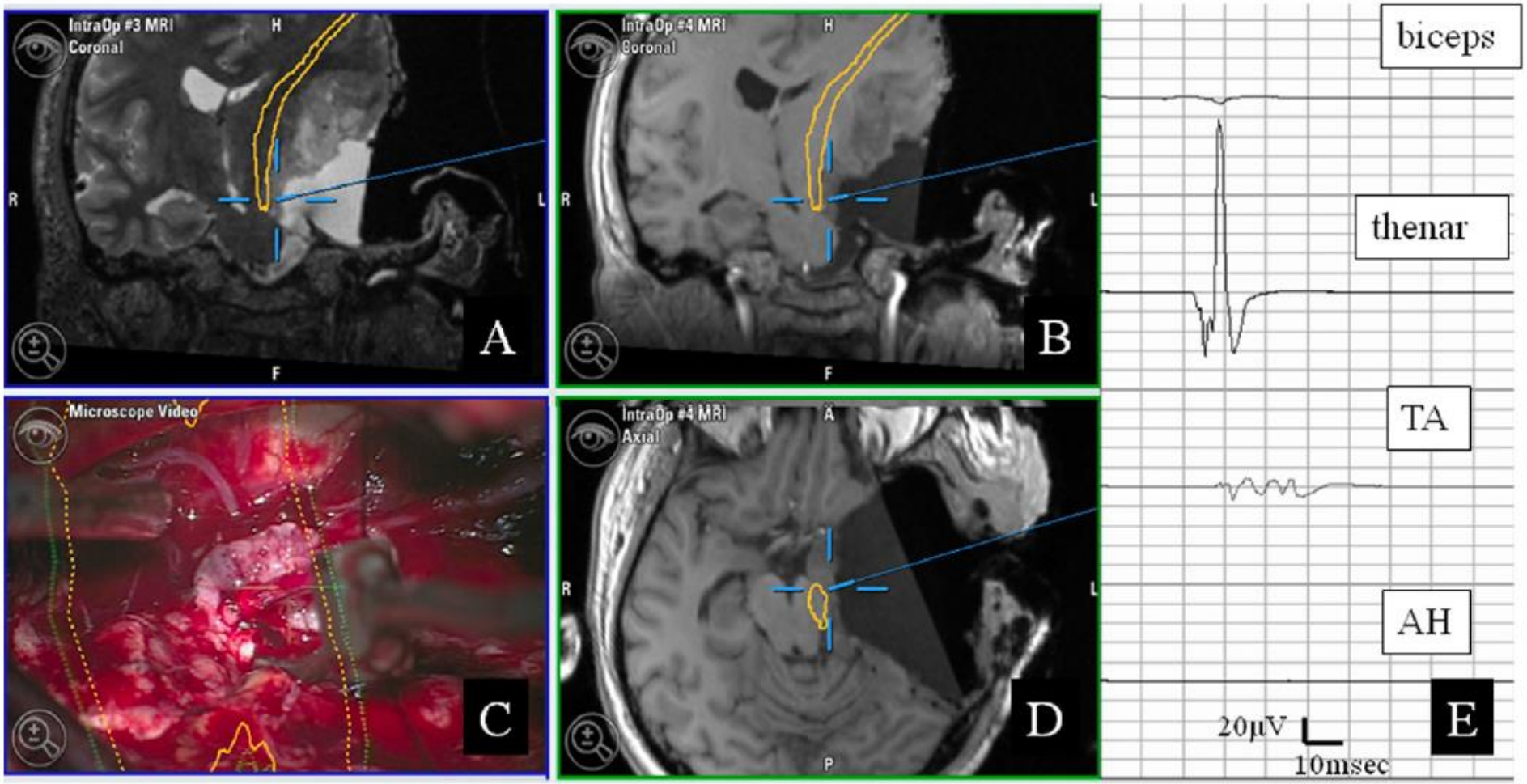


Figure 2. Photographs showing neuronavigation based on intraoperative images (**A,B,D**), a microscopic view with superposed objects (**C**), and associated motor-evoked potential recordings (**E**). The patient had a left temporal glioblastoma. During surgery neuronavigation indicated that intraoperative tractography of the pyramidal tracts (yellow lines) was close to the manipulating field (the center of blue cross). The object of the tracts was superimposed on the surgical field, and the bipolar stimulator was applied at the point where object of the tract was seen. Motor-evoked potential responses were obtained by direct subcortical stimulation. Biceps, biceps brachii muscles; thenar, thenar muscles; TA, anterior tibial muscles; AH, abuductor hallucis muscles.

Maesawa S et al. **World Neurosurgery**; 2010; 74 (1):153-61

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Impact of Intraoperative Stimulation Brain Mapping on Glioma Surgery Outcome: A Meta-Analysis

Philip C. De Witt Hamer, Santiago Gil Robles, Aeilko H. Zwinderman, Hugues Duffau, and Mitchel S. Berger

See accompanying editorial doi: 10.1200/JCO.2011.40.6959

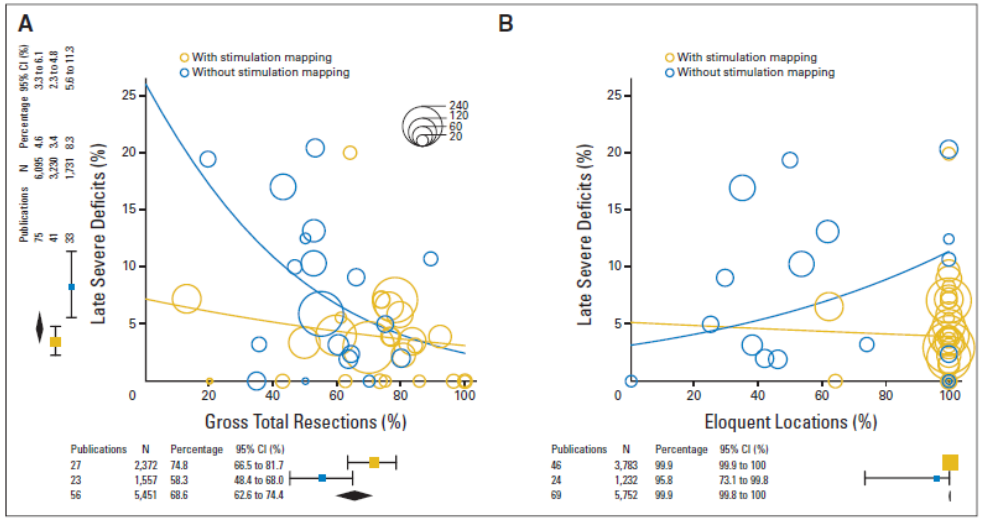
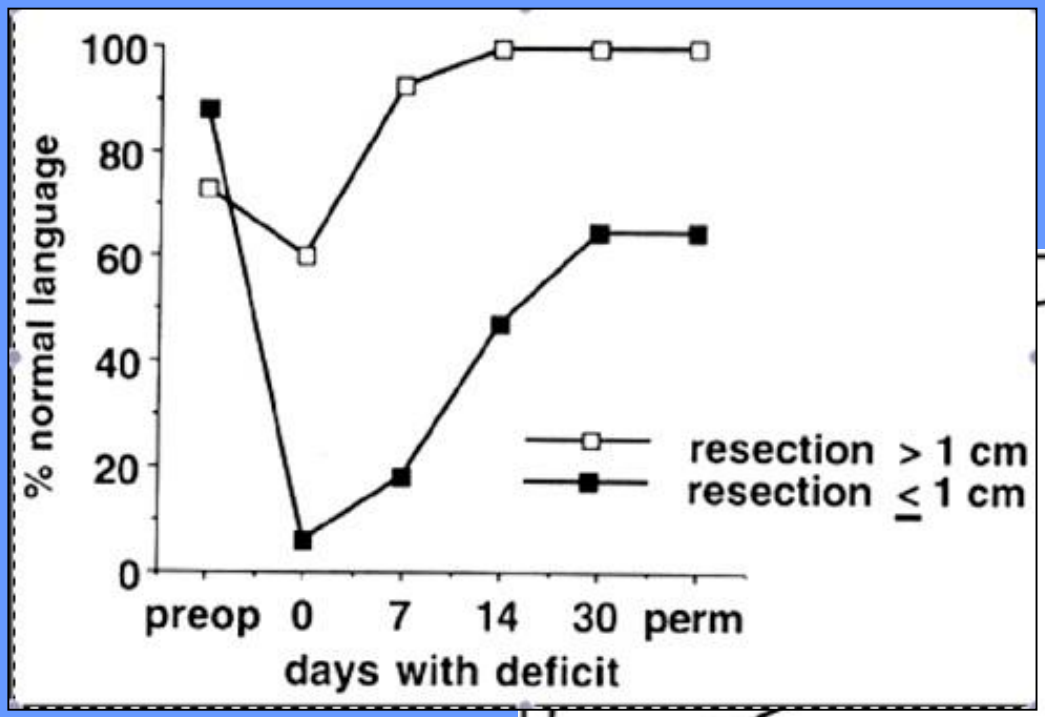


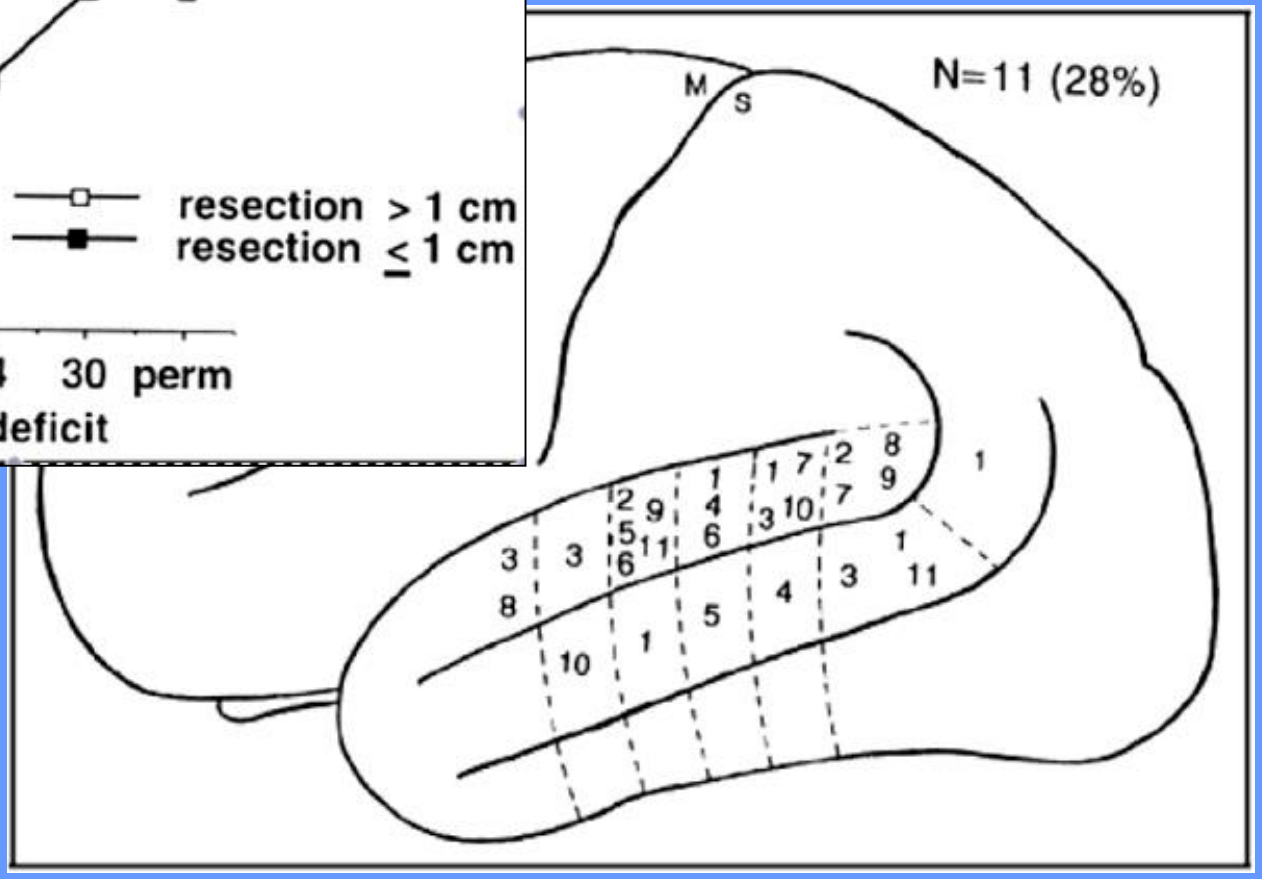
Fig 3. Glioma surgery outcome after resections with and without intraoperative stimulation mapping. (A) The relation between oncologic and neurologic outcome is plotted as a bubble chart with percentages of gross total resections (*x*-axis) and percentages of late severe neurologic deficits (*y*-axis) for patient populations after resection with (gold circles) and without (blue circles) intraoperative stimulation mapping. Sizes of circles are proportional to study cohort size. Regression lines are plotted. Lines are not straight because of inverse logit transformation. Summary estimates and 95% Bayesian CIs for all glioma resections (black diamonds), resections with intraoperative stimulation mapping (large gold squares), and without intraoperative stimulation mapping (small blue squares) are plotted and listed in the axis margins. (B) The relation between eloquent localization and neurologic outcome is plotted with percentage of eloquent localizations (*x*-axis) and percentages of late severe neurologic deficits (*y*-axis). Color codes, sizes of circles, and logistic regression lines are similar to those in (A).

Conclusion

Glioma resections using ISM are associated with fewer late severe neurologic deficits and more extensive resection, and they involve eloquent locations more frequently. This indicates that ISM should be universally implemented as standard of care for glioma surgery.

MAPPAGGIO INTRAOPERATORIO PER I TUMORI NELL AREA DEL LINGUAGGIO





Risultati peggiori per età più avanzata, donne, tumori ad alto grado e tumori estesi su due o più quadranti del lobo temporale

…aumenta l'EOR !!!!

Haglund Mi; Berger M; Shamseldin M; Lettich E; Ojemann G. **Neurosurgery** 1994; 34 (4): 567-76

CONTROLLO TAC/RMN SENZA E CON MDC POSTOPERATORIO

The British Journal of Radiology, 84 (2011), 271–278

Clinical target volume delineation in glioblastomas: pre-operative versus post-operative/pre-radiotherapy MRI

[1]P FARACE, PhD, [2]M G GIRI, [2]G MELIADÒ, [3]D AMELIO, MD, [3]L WIDESOTT, [4]G K RICCIARDI, MD, [5]S DALL'OGLIO, MD, [2]A RIZZOTTI, [1]A SBARBATI, MD, [4]A BELTRAMELLO, MD, [5]S MALUTA, MD and [3]M AMICHETTI, MD

[1]*Department of Morphological-Biomedical Sciences, Section of Anatomy and Histology, University of Verona, Italy,* [2]*Medical Physics Department, Borgo Trento Hospital, Verona, Italy,* [3]*ATreP, Provincial Agency for Protontherapy, Trento, Italy,* [4]*Neuroradiology Department, Borgo Trento Hospital, Verona, Italy and* [5]*Radiotherapy Department, Borgo Trento Hospital, Verona, Italy*

La RMN postoperatoria risulta più utile nella pianificazione della RT rispetto a quella preoperatoria

Inoltre ha
- Valore prognostico e
- Serve come feedback ai neurochirurghi

Progressi tecnologici

"Over the past 40 yers we have used the operating microscope, fluorescein fluorescence, ultrasonic imaging, image guided surgery, volumetric sterotaxy, intraoperative CT-guided surgery, and more recently, interventional magnetic resonance (MR) imaging…None of these past technical improvements has made a significant difference in the survival of patients harboring these lesions (and I do not believe that this one will either): *we just do not hurt patients as badly as we did 40 years ago*"

Kelly PJ, J Neurosurg, 2004

Entità dell'asportazione e KPS

CI SONO ANCHE

ALTRE VARIABILI CHE INFLUENZANO LA SOPRAVVIVENZA,

CHIRURGO ‘INDIPENDENTI’

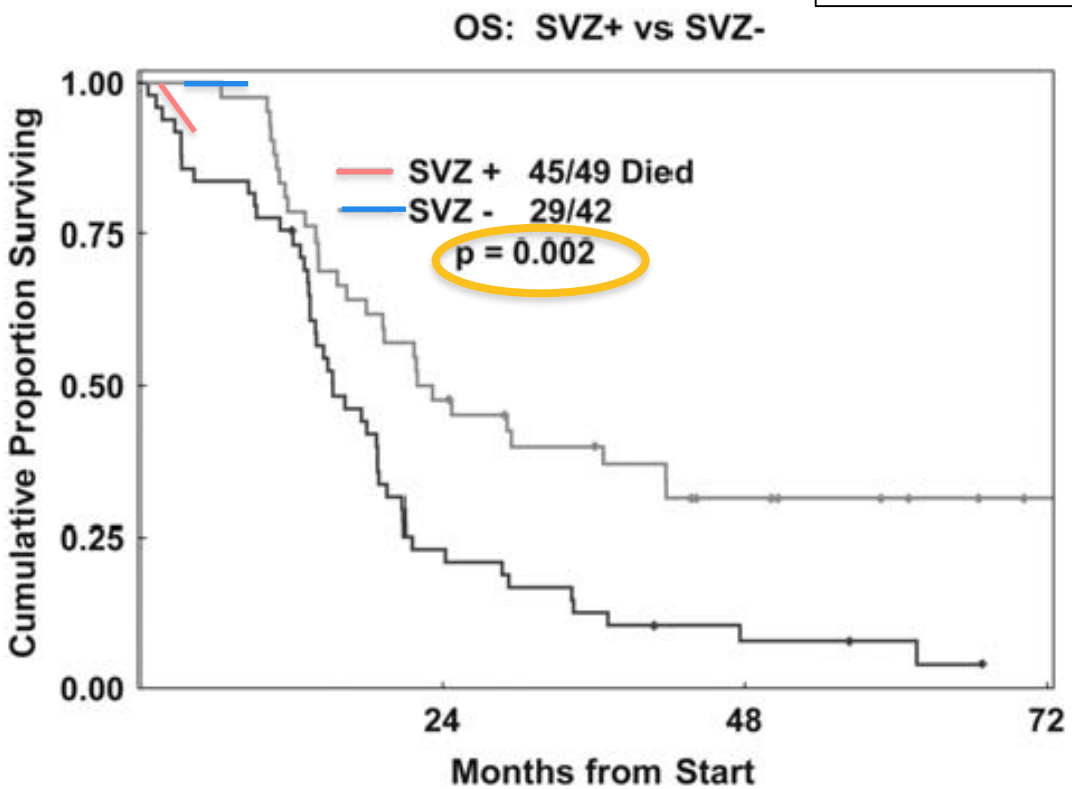
LA SEDE CORRELA CON LA PROGNOSI

NON SOLO PER LA EOR

Zona Subventricolare

..reclutamento delle staminali residenti da parte del tumore

TIPO I: contatto sia con SVZ sia con corteccia
TIPO II: contatto solo con SVZ
TIPO III: contatto solo con corteccia
TIPO IV: non contatto né con SVZ né con corteccia



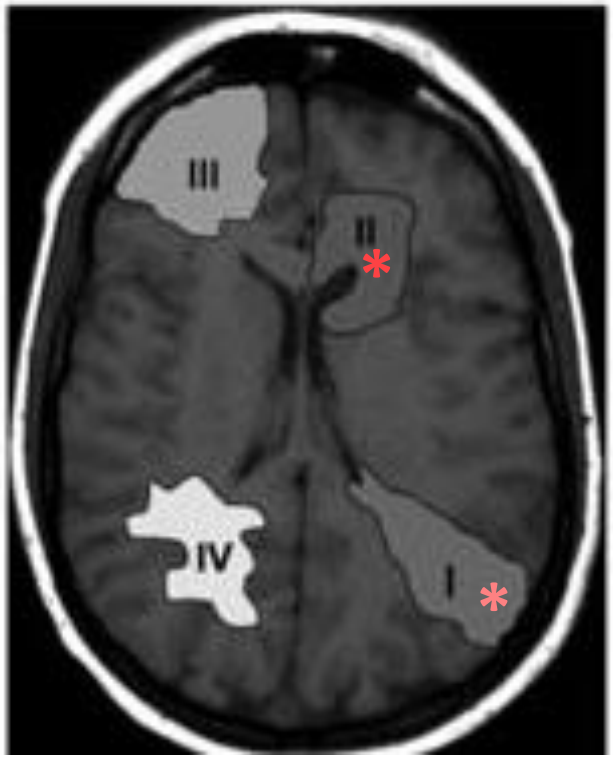


Fig. 6. Kaplan-Meier curve demonstrating survival difference between SVZ-positive and SVZ-negative tumors.

INDIPENDENTEMENTE DALLA EOR!!!!

Jafri NF et al. **Neuro-Oncology** 2012- UNIV. of S.FRANCISCO

ALTRE CARATTERISTICHE DEL PAZIENTE

Surgical outcomes for older patients with glioblastoma multiforme: preoperative factors associated with decreased survival

Clinical article

Kaisorn L. Chaichana, M.D.,[1,2,4] Khan K. Chaichana, B.S.,[1,2,4]
Alessandro Olivi, M.D.,[1,2,4] Jon D. Weingart, M.D.,[1,2,4] Richard Bennett, M.D.,[3]
Henry Brem, M.D.,[1,2,4] and Alfredo Quiñones-Hinojosa, M.D.[1,2,4]

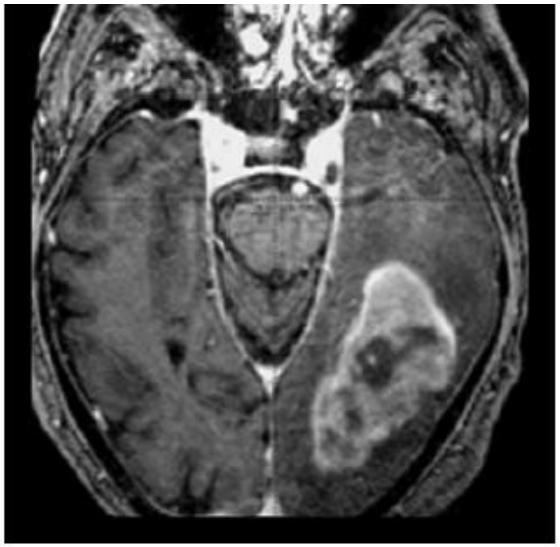
Departments of [1]Neurosurgery, [2]Oncology and [3]Medicine, [4]The Johns Hopkins Neuro-Oncology Surgical Outcomes Research Laboratory, Johns Hopkins University and School of Medicine, Baltimore, Maryland

TABLE 3: Multivariate associations with survival for patients older than 65 years undergoing resection of an intracranial GBM

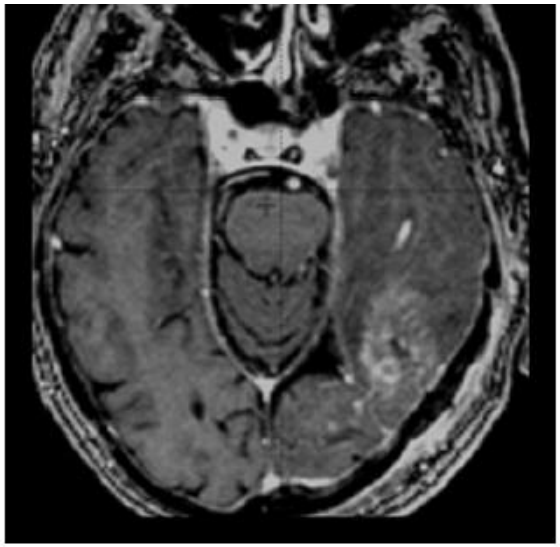
Multivariate Associations w/ Survival		
Variables	OR (95% CI)	p Value*
factors associated w/ decreased survival		
KPS score <80	1.756 (1.431–2.754)	0.001
COPD	3.762 (1.350–9.061)	0.01
motor deficit	3.480 (1.279–7.993)	0.01
language deficit	2.311 (1.310–3.960)	0.005
cognitive deficit	1.792 (1.089–2.916)	0.02
tumor size	1.189 (1.018–1.358)	0.01
tumor size >4 cm	1.982 (1.264–3.142)	0.002

J Neurosurg 114:587–594, 2011

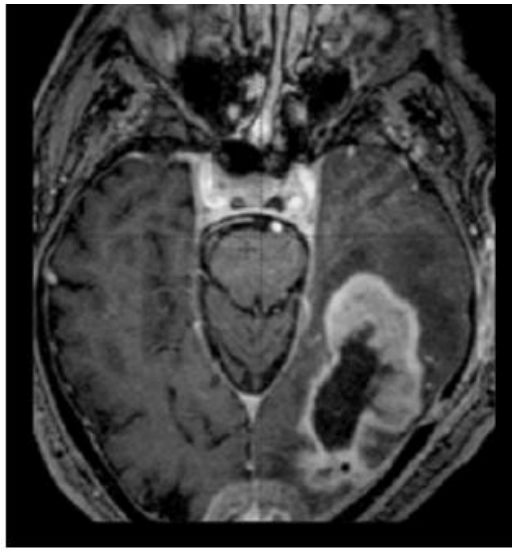
TRATTAMENTO POSTOPERATORIO



preop



postop



Pre-RT

DA: Farace P et al. Br J Radiol. 2011 Mar;84(999):271-8. Clinical target volume delineation in glioblastomas: pre-operative versus post-operative/pre-radiotherapy MRI.

Importante il TIMING del trattamento!!!!
Evitare lunghe attese che si traducono in crescita tumorale

CARATTERISTICHE MOLECOLARI

Quasi 'classiche':

MGMT (0-6-metilguanine-DNA-metiltransferasi)

Proteina di riparazione del DNA.
Rimuove l'alchilazione dalla posizione O^6 della guanina
Cioè vanifica la lesione più tossica indotta dagli alchilanti (es. TMZ)
Se il promotore di MGMT è metilato, MGMT non è espresso.

Friedman HS et al. - J Clin Oncol 1998; 16: 3851-7
Esteller et al. NEJM 2000; 343: 1350-4

IDH 1 / 2 (isocitrato deidrogenasi 1 e 2)

La mutazione di questo gene conferisce un vantaggio funzionale alla protiena:
Dovuta ad alterata substrat- specificità
che risulta
in aumentata produzione diD2-isdrossiglutarato (anziché l'alfa ketoglutarato) che
Agisce come oncometabolita

Turcan S et al.- Nature 2012; 483: 479-83

Weller M; Stupp R; et al. **Neuro-Oncology** 2012 iv100-8

METILAZIONE DEL PROMOTORE MGMT

- omogenea all'interno del glioma
- non cambia durante il corso della malattia (in genere)
- + prognostica nei pazienti con glioma anaplastico
- che ricevono RT o CT o entrambe *(NOA-04, EORTC 26951)*
- utilizzabile come marcatore predittivo per il clinical decision making *:*

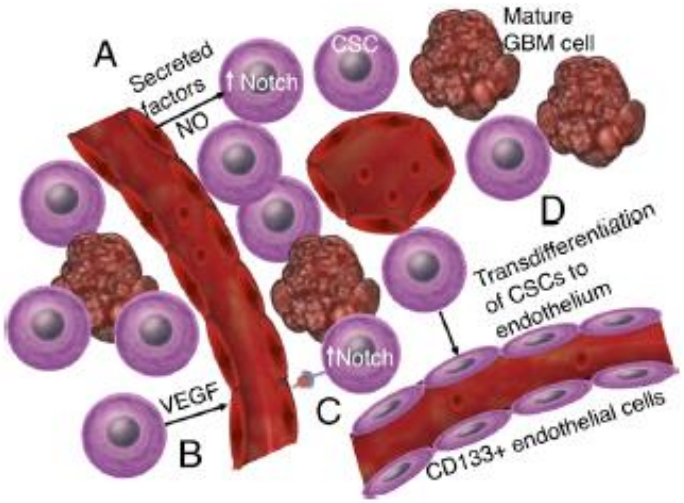
  predice il beneficio da CT con agenti alchilanti (EORTC 26981) ed è particolarmente utile nei pazienti anziani con glioblastoma (NOA-08, Nordic trial)

MUTAZIONI DI IDH 1/2

- IDH 1 / 2 spesso espresso nei gliomi di grado II e III e può aiutare nella diagnosi differenziale vs la gliosi reattiva ed altre entità di gliomi (astrocitoma pilocitico, ganglioglioma ed ependimoma che tipicamente non hanno mutazioni IDH 1 /2)
- lo stato IDH 1 / 2 è omogeneo all'interno dei gliomi
- le mutazioni IDH 1 / 2 sono prognosticamente favorevoli, specie nei gradi WHO III e IV

Weller M; Stupp R; et al. **Neuro-Oncology** 2012 iv100-8

Oltre ai marcatori molecolari,
Svolge un ruolo cruciale nella radio e chemioresistenza
la presenza di cellule staminali tumorali



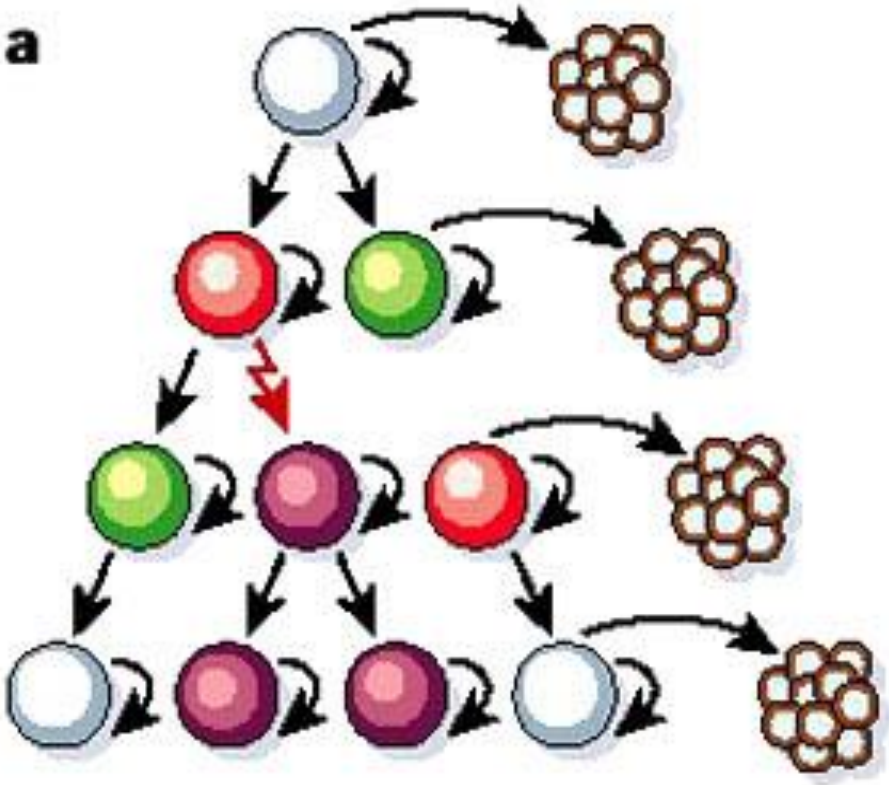
REVIEW ARTICLE

Glioblastoma Cancer Stem-Like Cells

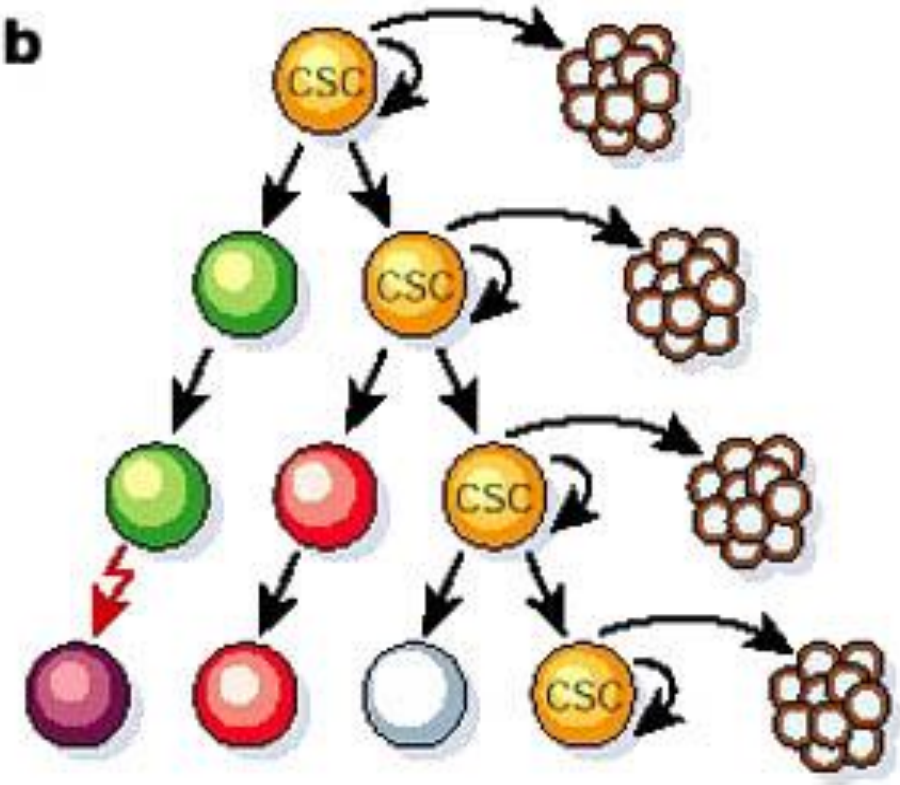
Implications for Pathogenesis and Treatment

Edjah Kweku-Ebura Nduom, MD, Costas George Hadjipanayis, MD, PhD,*†‡ and Erwin G. Van Meir, PhD*§||¶#*

The Cancer Journal • Volume 18, Number 1, January/February 2012

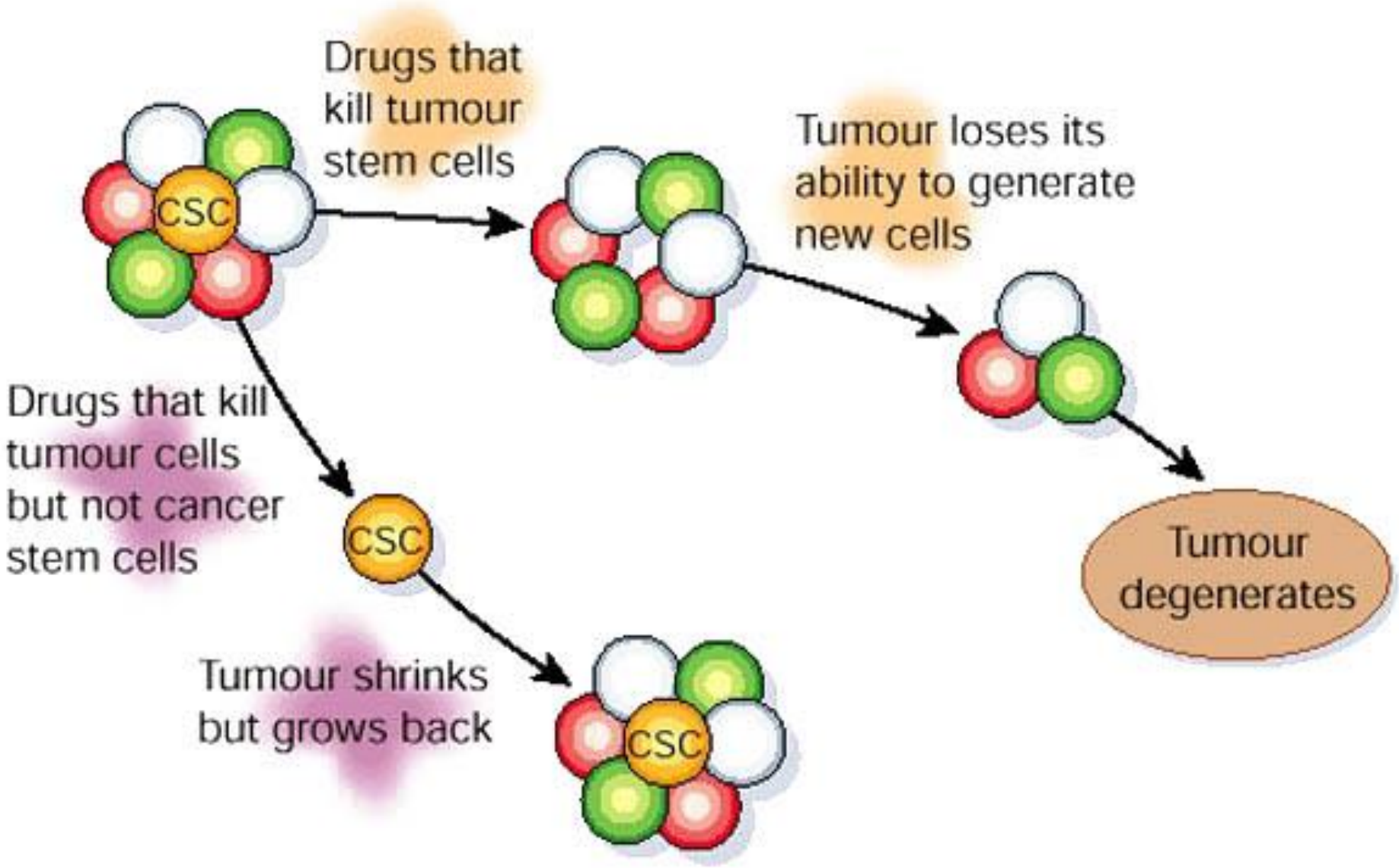


Tumour cells are heterogeneous, but most cells can proliferate extensively and form new tumours



Tumour cells are heterogeneous and only the cancer stem cell subset (CSC; yellow) has the ability to proliferate extensively and form new tumours

Reya et al. Nature 414, 105-111 (2001)



Reya et al. Nature 414, 105-111 (2001)

STEM CELLS®
CANCER STEM CELLS

SOX2 Silencing in Glioblastoma Tumor Initiating Cells Cau of Proliferation and Loss of Tumorigenicity

Rosaria Maria Rita Gangemi[1], Fabrizio Griffero[1,2], Daniela Marubbi[1,2], Marzia Pe
Cristina Capra[1], Paolo Malatesta[1,2], Gian Luigi Ravetti[3], Gian Luigi Zona[4], ...to
Giorgio Corte[1,2*]

[1]Istituto Nazionale per la Ricerca sul Cancro; [2]Dipartimento di Oncologia Biologia
[3]Anatomia Patologica Ospedaliera, Ospedale S. Martino, Dipartimento di Neuros
Università di Genova, Largo R. Benzi 10 16132 Genova, Italy.

Key words. Glioblastoma • Tumor initiating cells • SOX2 gene silencing •

J Cancer Res Clin Oncol (2012) 138:35–47
DOI 10.1007/s00432-011-1070-5

ORIGINAL PAPER

Quantitative methylation analysis of *HOXA3*, *7*, *9*, and *10* genes in glioma: association with tumor WHO grade and clinical outcome

Angela Di Vinci · Ida Casciano · Elena Marasco · Barbara Banelli · Gian Luigi Ravetti · Luana Borzì · Claudio Brigati · Alessandra Forlani · Alessandra Dorcaratto · Giorgio Allemanni · Gianluigi Zona · Renato Spaziante · Henning Gohlke · Giovanni Gardin · Domenico Franco Merlo · Vilma Mantovani · Massimo Romani

Different Response of Human Glioma Tumor-initiating Cells to Epidermal Growth Factor Receptor Kinase Inhibitors*[S]

THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 284, NO. 77, pp. 1–xxx, 7777 77, 2009
Printed in the U.S.A.

Received for publication, September 15, 2008, and in revised form, January 14, 2009 Published, JBC Papers in Press, January 14, 2009, DOI 10.1074/jbc.M807111200

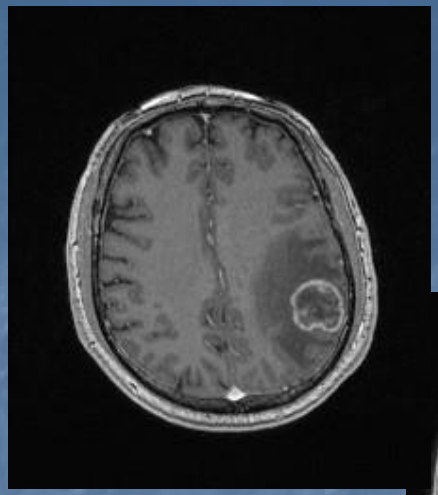
Fabrizio Griffero[‡§], Antonio Daga[‡], Daniela Marubbi[§], Maria Cristina Capra[‡], Alice Melotti[‡§], Alessandra Pattarozzi[§], Monica Gatti[§], Adriana Bajetto[§], Carola Porcile[§], Federica Barbieri[§], Roberto E. Favoni[‡], Michele Lo Casto[‡], Gianluigi Zona[¶], Renato Spaziante[¶], Tullio Florio[§1,2], and Giorgio Corte[‡§1,3]

From the [‡]Department of Translational Oncology, National Institute for Cancer Research, 16132 Genova and [§]Department of Oncology, Biology and Genetics and [¶]Department of Neuroscience, Oph... ology and Genetics, University of Genova, 16132 Genova, Italy

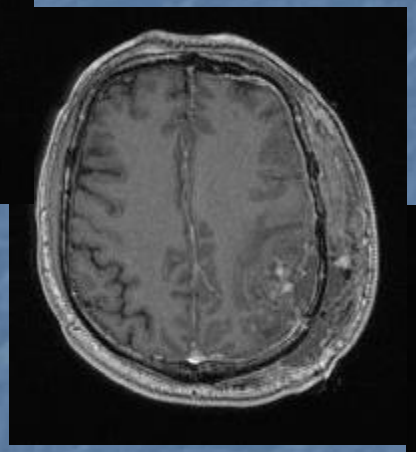
Comparative Analysis of DNA Repair in Stem and Nonstem Glioma Cell Cultures

Monica Ropolo,[1] Antonio Daga,[2] Fabrizio Griffero,[2] Mara Foresta,[1] Gianluigi Casartelli,[1] Annalisa Zunino,[3] Alessandro Poggi,[4] Enrico Cappelli,[5] Gianluigi Zona,[6] Renato Spaziante,[6] Giorgio Corte,[2,7] and Guido Frosina[1]

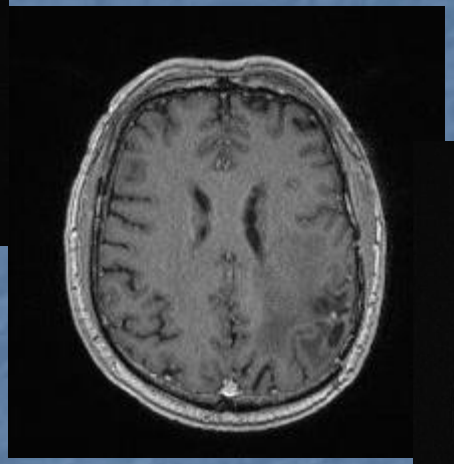
[1]Molecular Mutagenesis and DNA Repair, [2]Gene Transfer, [3]Cytogenetics, and [4]Immunology Laboratories, Istituto Nazionale Ricerca Cancro; [5]Department of Pediatric Hemato-Oncology, Istituto Giannina Gaslini; [6]Section of Neurosurgery, Department of Neuroscience, Ophthalmology and Genetics, and [7]Department of Oncology Biology and Genetics, University of Genova, Genova, Italy



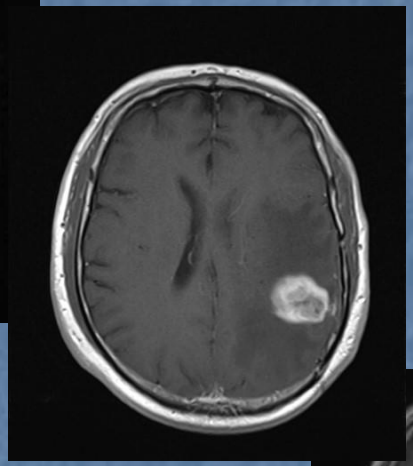
2016



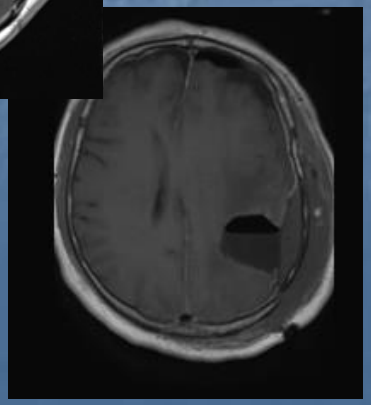
Post-op



2017



2018



Post-op

Maschio, 55 anni
IDH 1-2 WT
Metiilato
LOH 1 p/19 q
KPS 100

La lutte elle-même vers les sommets suffit à remplir un coeur d'homme.
Il faut imaginer Sisyphe heureux.

Albert Camus, *Le Mythe de Sisyphe*

Ruolo della chirurgia

Estensione della resezione chirurgica

Journal of Neuro-Oncology **42:** 227–231, 1999.

Extent of resection as a prognostic variable in the treatment of gliomas

Kenneth R. Hess
Department of Biomathematics, M.D. Anderson Cancer Center, Houston, TX 77030-4095, USA

Criticism:

resezione maggiore in aree non eloquenti

differente distribuzione delle covarianti

differenti criteri di classificazione

differente selezione di pazienti

varie "imperfezioni" metodologiche

studi retrospettivi non randomizzati

Studio prospettici randomizzati (Classe evidence I) non eticamente possibili

Ruolo della chirurgia

Estensione della resezione chirurgica

J Neurosurg 95:190–198, 2001

A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival

Michel Lacroix, M.D., Dima Abi-Said, Ph.D., Daryl R. Fourney, M.D., Ziya L. Gokaslan, M.D., Weiming Shi, M.D., Franco DeMonte, M.D., Frederick F. Lang, M.D., Ian E. McCutcheon, M.D., Samuel J. Hassenbusch, M.D., Ph.D., Eric Holland, M.D., Ph.D., Kenneth Hess, Ph.D., Christopher Michael, M.D., Daniel Miller, M.D., and Raymond Sawaya, M.D.

Department of Neurosurgery, The University of Texas M. D. Anderson Cancer Center, Houston, Texas

Fattore prognostico indipendente

≥ 98%	*ST 13 mesi*
< 98%	*ST 8.8 mesi*

Ruolo della chirurgia

Estensione della resezione chirurgica

"As a prognostic factor in maligant glioma, however, the extent of the surgical resection falls far behind factors over which a surgeon has not control: tumor grade, patient age and KPS score. In some studies, surgery does not even make it onto the radar screen of statistical significance"

Kelly PJ, J Neurosurg, 2004

Ruolo della chirurgia

Estensione della resezione chirurgica

J Neurosurg 99:467–473, 2003

Survival following surgery and prognostic factors for recently diagnosed malignant glioma: data from the Glioma Outcomes Project

EDWARD R. LAWS, M.D., IAN F. PARNEY, M.D., PH.D., WEI HUANG, M.S., FRED ANDERSON, PH.D., ANGEL M. MORRIS, B.S.N., ANTHONY ASHER, M.D., KEVIN O. LILLEHEI, M.D., MARK BERNSTEIN, M.D., HENRY BREM, M.D., ANDREW SLOAN, M.D., MITCHEL S. BERGER, M.D., SUSAN CHANG, M.D., AND THE GLIOMA OUTCOMES INVESTIGATORS

Fattore prognostici favorevoli:

Resezione vs biopsia	*($p < 0.0001$)*
Eta ≤ 60	*($p < 0.0001$)*
KPS ≥ 70	*($p = 0.0004$)*

Studio osservazionale 788 gliomi maligni (Classe evidence II)

CORRELAZIONE TRA PERCENTUALE DI RESEZIONE E SOPRAVVIVENZA

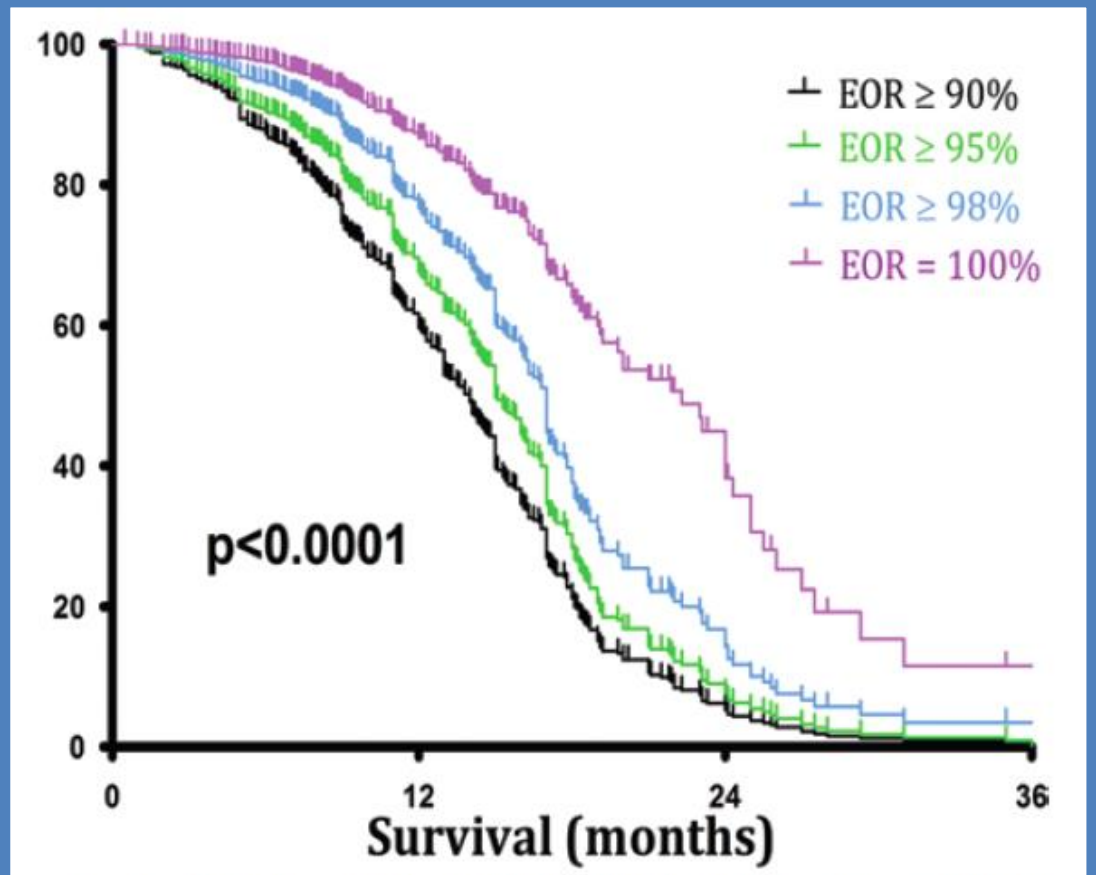


FIG. 4. Stepwise improvement in overall survival when comparing 90%, 95%, 98%, and 100% EOR thresholds.

J Neurosurg 115:3–8, 2011

NADER SANAI, M.D.,[1] MEI-YIN POLLEY, PH.D.,[2] MICHAEL W. MCDERMOTT, M.D.,[1] ANDREW T. PARSA, M.D., PH.D.,[1] AND MITCHEL S. BERGER, M.D.[1]

[1]Brain Tumor Research Center, and [2]Division of Biostatistics, Department of Neurological Surgery, University of California, San Francisco, California

Quanto sopra giustificherebbe la chirurgia citoriduttiva, e sopratutto la GTR

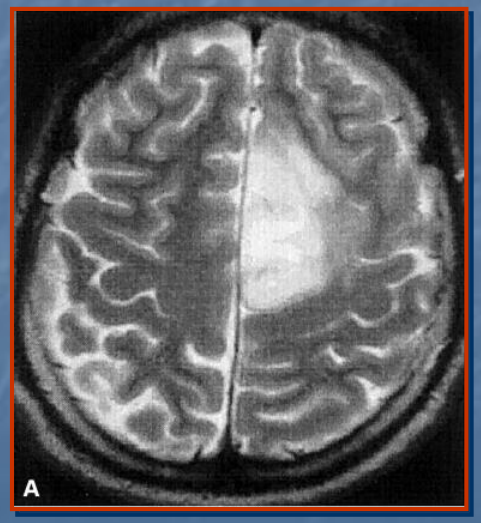
Inoltre con un debulking è possibile ottenere molto più tessuto da analizzare e quindi diminuire il rischio di sbagliare diagnosi *(affidabilità biopsia sterotassica !!)*

82.6% in aree critiche

Spesso pz. **PAUCISINTOMATICi**

EPILESSIA ben controllata

RADICALITÀ impossibile



•L’imaging funzionale ha dimostrato che non solo esiste una variabilità anatomo-funzionale interindividuale ma anche una plasticità neuronale che permette una redistribuzione a lungo e breve termine delle mappe funzionali cerebrali:

- Plasticità naturale (apprendimento e memoria)
- Plasticità post-lesionale (stroke o traumi)

• I GLIOMI *(soprattutto LGG)* inducono una riorganizzazione delle funzioni cerebrali in una misura ASSOLUTAMENTE INDIVIDUALE

• Lo studio dell’interazione Lesione-Cervello e della riorganizzazione funzionale è fondamentale per il planning chirurgico

- L’esame non invasivo più usato è l’RM funzionale: basandosi sul BOLD spesso non è possibile ottenere informazioni sulla zona occupata dal tumore a causa delle differenti caratteristiche vascolari e metaboliche del tessuto tumorale

- Non riesce a differenziare aree essenziali da aree “sostituibili” (SMA)

- In pratica l’fRM non ci dà la certezza dell’assenza di funzione all’interno del tumore

- E’ comunque un grande aiuto per “inquadrare” preoperatoriamente le aree critiche di un paziente

Allo stato attuale il metodo più efficace e sicuro per testare le funzioni corticali e sottocorticali è la STIMOLAZIONE ELETTRICA DIRETTA (DES)

1954 Penfield
1987 Ojemann

- Funzione motoria (in ANESTESIA GENERALE) provocando movimenti involontari

- Funzione sensitiva e funzioni cognitive (linguaggio, calcolo, lettura, memoria) in ANESTESIA LOCALE provocando dei disturbi transitori di una funzione → parestesie, anartria, anomia, acalculia, “speech arrest” etc...

- In pazienti selezionati, il brain mapping consente di rimuovere lesioni in area critica rilevando le zone di corteccia funzionali (e quindi da evitare) o mostrando l'assenza di funzione in zone infiltrate dal tumore.

- Se è prevedibile che il volume del residuo residuo post-chirurgico > 10 cm^3, chirurgia utile ??

- I punti di repere anatomici "superficiali" o "standard" non sono sufficienti visto che l'area motoria primaria può estendersi più di 20 mm avanti o dietro la scissura di Rolando soprattutto in presenza di tumori in tale regione. Le variazioni interindividuali sono molto frequenti

- Le zone del linguaggio sono ancora più variabili in sede e distribuzione

- In generale una stimolazione negativa consente di predire con buona precisione l'assenza di funzione in una data area

Ruolo della chirurgia

Prospettive future

"Current understanding in tumor biology has opened new avenues to the treatment of malignant glioma patients by inhibiting cell proliferation, inducing cell death, and blocking neoangiogenesis or restoring an appropriate immune response"

Terapia genetica? (HSV-tk Gancyclovir)
Convection delivery?
Immunotherapia?
Anti-angiogenesi?
Inibizione delle cellule staminali del tumore?

Dietrich PY and de Tribolet N, Neurosurg focus, 1997

Progressi tecnologici

"Over the past 40 yers we have used the operating microscope, fluorescein fluorescence, ultrasonic imaging, image guided surgery, volumetric sterotaxy, intraoperative CT-guided surgery, and more recently, interventional magnetic resonance (MR) imaging…None of these past technical improvements has made a significant difference in the survival of patients harboring these lesions (and I do not believe that this one will either): we just do not hurt patients as badly as we did 40 years ago"

Kelly PJ, J Neurosurg, 2004

Entità dell'asportazione e KPS

SPECIAL ARTICLE

The Neurosurgeon as Local Oncologist: Cellular and Molecular Neurosurgery in Malignant Glioma Therapy

Ian F. Dunn, M.D.
Brain Tumor Laboratories and Departments of Neurosurgery, Brigham and Women's Hospital, Children's Hospital, and Harvard Medical School, Boston, Massachusetts

Peter McL. Black, M.D., Ph.D.
Brain Tumor Laboratories and Departments of Neurosurgery, Brigham and Women's Hospital, Children's Hospital, and Harvard Medical School, Boston, Massachusetts

Reprint requests:
Peter McL. Black, M.D., Ph.D., Department of Neurosurgery, Children's Hospital of Boston, Bader 3, 300 Longwood Avenue, Boston, MA 02115.
Email: pblack@partners.org

Received, August 21, 2002.
Accepted, February 12, 2003.

- **Bioreactors**
  - *Read TA et al, Nat Biotechnol, 2001*
- **Cellule staminali neuronali (NSC)**
  - *Ehtesham M et al, Neurosug Focus, 2005*
  - *Sanai N et al, N Engl J Med, 2005*
- **Immunoterapia**
  - *Dietrich PY et al, J Immunol, 2000*
  - *Zeltner PM et al, Child Nerv Syst,1999*
- **Polimeri biodegradabili**
  - *Brem H et al, Lancet, 1995*
  - *Westphal M et al, Neuro-oncol, 2003*
- **Convection enhanced drug delivery**
  - *Bobo RH et al, Proc Natl Acad Sci USA, 1994*
  - *Laske DW et al, J Neurosurg, 1997*
  - *Boiardi A et al, J Neurooncol, 2001*

Conclusioni minime

- **Necessario stratificare i pazienti nella valutazione prognostica di un determinato istotipo, nella costruzione dei futuri trials e per delineare la migliore strategia terapeutica per ogni singolo caso**
- **Se possibile (?) studi randomizzati prospettici nei pazienti "low-risk" tra GTR e "wait and see" (LGG)**
- **Sono comunque candidati alla chirurgia precoce i pazienti "high risk"** ***(lesioni più grandi, sintomi neurologici ± crisi, "contrast enhancement" positivo)***
- **Nella pratica clinica bisogna selezionare la soluzione più adeguata per ogni singolo paziente ("tailoring") considerando**
  - **Fattori prognostici del tumore e del paziente**
  - **Qualità della vita e condizioni neurologiche**
  - **Eventuali deficit neurologici aggiuntivi**
  - **Strategie terapeutiche multimoidali (adiuvanti e neo-adiuvanti)**

Considerazioni finali

- Chirurgia "frustrante"
  - Sopravvivenza invariata nel corso degli ultimi trenta anni, nonostante i progressi della tecnica che hanno ridotto la morbidità
  - Necessario stratificare i pazienti nella valutazione prognostica di un determinato istotipo, nella costruzione dei futuri trials e per delineare la migliore strategia terapeutica per ogni singolo caso
- Qualità di vita (KPS)
  - Entità dell'asportazione proporzionata al danno
- Prognosi legata a markers molecolari e genetici
  - (ampl. EGFR, eterozigosi cromosoma 10 vs 19, MIB-1 etc)
- Trattamento multimodale e terapia traslazionale
  - Team multispecialistico

JM Piepmeyer, Clin Neurosurg, 1998

See the corresponding article in this issue, pp 287–294.

J Neurosurg 101:284–286, 2004

Editorial

Technology in the resection of gliomas and the definition of madness

Patrick J. Kelly, M.D.

Department of Neurological Surgery, New York University School of Medicine, New York, New York

Someone once defined madness as doing the same thing over and over again , expecting a different result. Year after year we develop new technological methods…that enable us to resect larger portions of a glioma more accurately. Despite these efforts, patients continue to die of recurrent disease… At best our procedures may have prolonged mean survival in patients with GBM from 37.5 to 50.5 weeks.

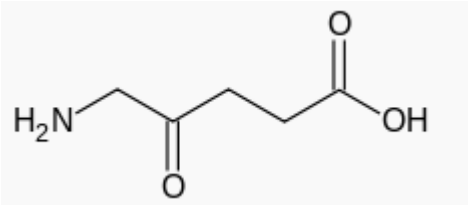
The evolution for FL400

-Intense Blue

-400W Bulb
-SAI

-400W Bulb
-SAI (Small angle)
-Superior Optics
(Increased transfer light)

5-ALA Aminolevulinic acid /GLIOLAN



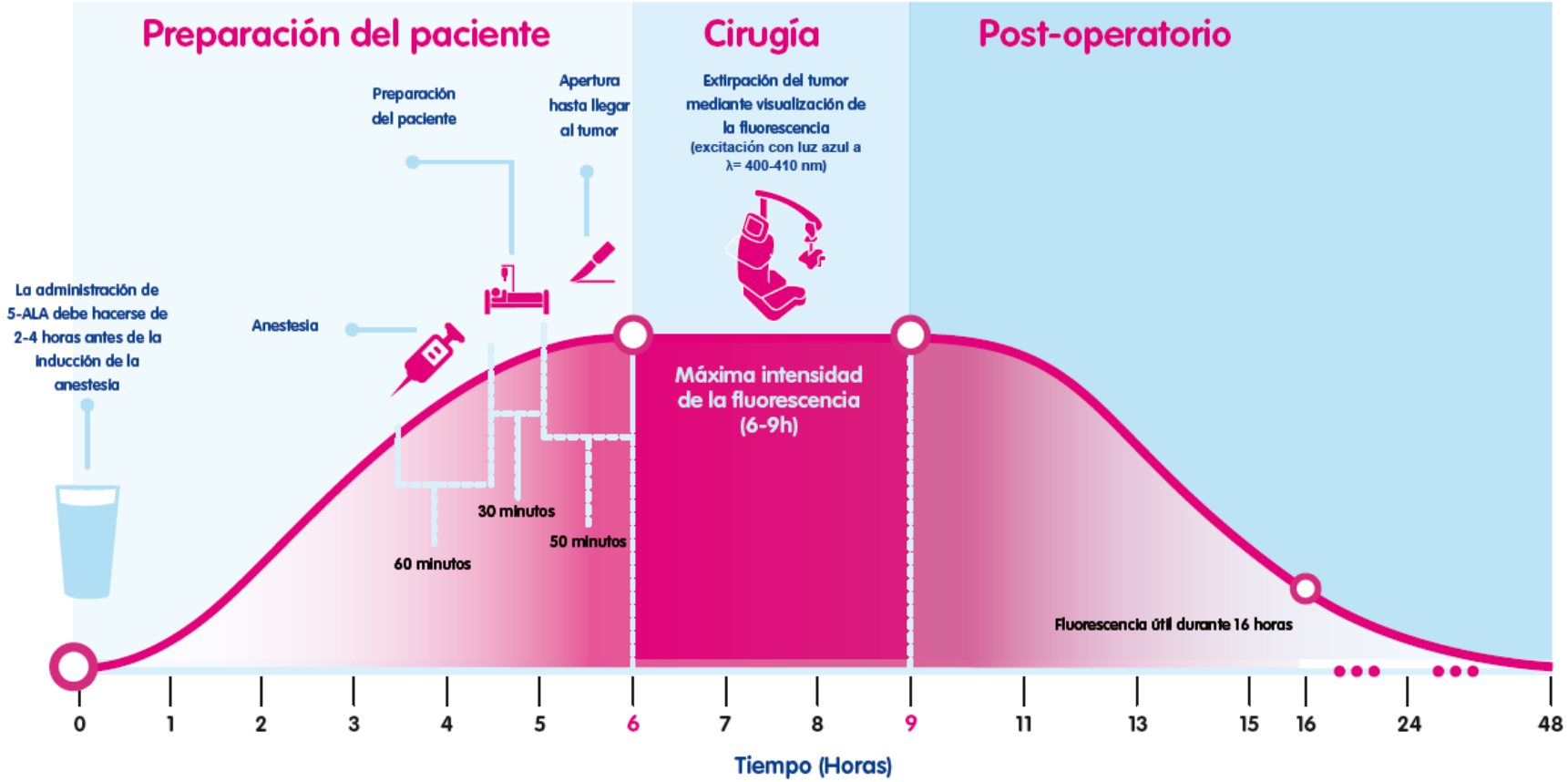
1-GLIOLAN is an orally administered drug given preoperatively to patients undergoing surgery to resect malignant high grade glioma (III IV)

2-The recommended dose of Gliolan is 20 mg per kilogram body weight, taken two to four hours before the patient is anaesthetised. Gliolan powder is dissolved in 50 ml tap water before the patient drinks the solution

3-It is absorbed by cells in the body, where it is converted by enzymes into protoporphyrin IX (PPIX). Since glioma cells take up more of the active substance and convert it more rapidly into PPIX, higher levels of PPIX accumulate in the cancer cells than in normal tissue. When illuminated under blue light of a specific wavelength, the PPIX in the tumour glows an intense red, while the normal brain tissue appears blue

Name: Gliolan
EMEA Product number: EMEA/H/C/000744
Active substance: 5-aminolevulinic acid hydrochloride
ATC Code: L01XD04
Marketing Authorisation Holder: medac GmbH

gliolan®
(aminolevulinic acid HCl)


Preparación del paciente
Cirugía
Post-operatorio
Preparación del paciente
Apertura hasta llegar al tumor
Extirpación del tumor mediante visualización de la fluorescencia (excitación con luz azul a λ= 400-410 nm)
La administración de 5-ALA debe hacerse de 2-4 horas antes de la inducción de la anestesia
Anestesia
Máxima intensidad de la fluorescencia (6-9h)
30 minutos
50 minutos
60 minutos
Fluorescencia útil durante 16 horas
0
1
2
3
4
5
6
7
8
9
11
13
15
16
24
48
Tiempo (Horas)

OPTIMIZING DEMONSTRATION AT THE OR / FL400

1- Organize one day presentation
2- Planify Schedule with surgeon

PLANIFICACIÓN DEMONSTRACIÓN LEICA OH6 M30 "FULLY LOADED" :

- ✓Día 29/ Octubre : Instalación y Calibración + Cirugía Quiróf;
- ✓Día 30-31/ Octubre : Aplicaciones en Quirófano + Fluorescencia Intra-Operatória;
- ✓Día 01-011/ Noviembre : Soporte técnico en Quirófano;
- ✓Día 12/ Octubre : Desmontaje.

***Especialista de producto:** Alex Badia
***Responsable SAT Demo:** Jordi Meseguer
***Costumer Care Support:** Ana Marquez
***Logistica y transporte:** Oscar Vigara

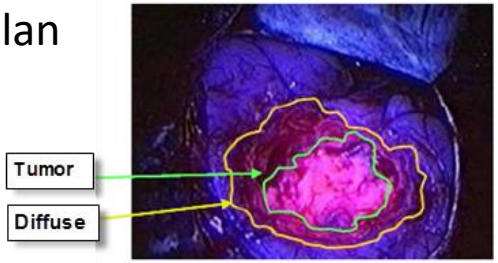
3- Contact with MEDAC or Gliolan local distributor / depending

AT THE OR

4-Check the functionality of the FL400 mode (presets)
5-Check the life time of the lamps (after 50hrs of use Fluo signal is decreasing by 50%)
6-Check that all filters are in/out while activating
7-Check during the surgery that WD and magnification are as low as possible
5-Check you have the latest scene files for the FL mode of the camera

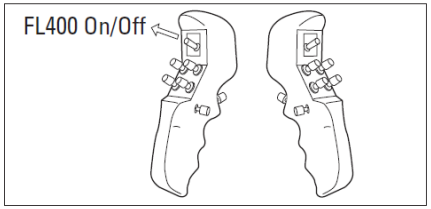
Prior considerations before using Gliolan

- Microscope must be equipped with de Module FL400
- Necessary that surgeon is certified for the use of Gliolan

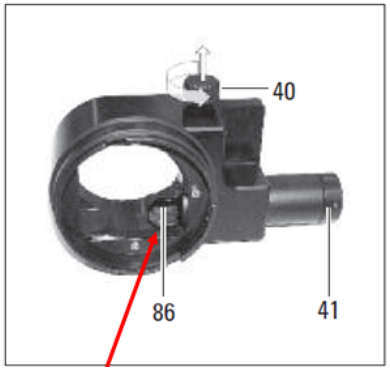


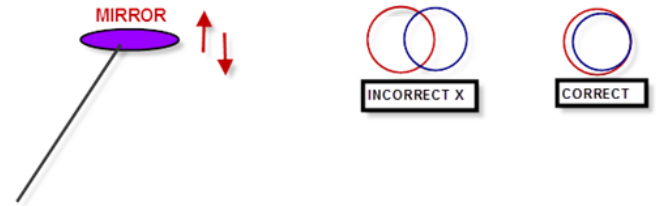
- Configuration for activating Filters has to be programmed and settled

Control de las funciones del FL400



- Check Camera Settings
- Protocol review prior before surgery with nurses
- Depending on the model, make surefor that system is optimized (OH4)

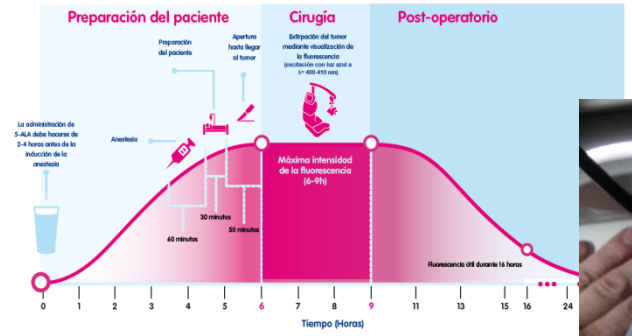


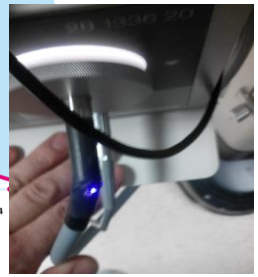


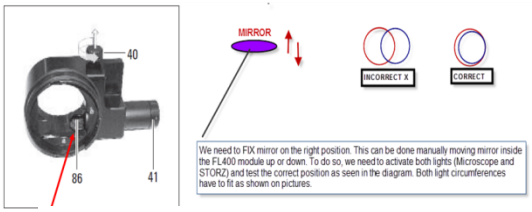
We need to FIX mirror on the right position. This can be done manually moving mirror inside the FL400 module up or down. To do so, we need to activate both lights (Microscope and STORZ) and test the correct position as seen in the diagram. Both light circumferences have to fit as shown on pictures.

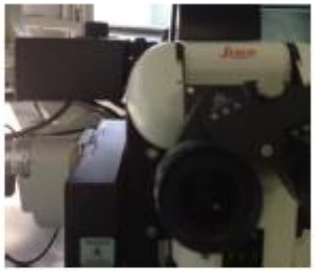
M525OH4 / M720OH5

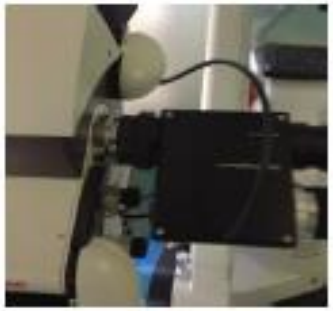
- Review Administration Protocol
- Fiber Optics Cable Review STORZ
- OH4 FL400 module review mirrors
- Check Camera Positions
- Lamp Life Review
- Select Best Lamp life unit (1)
- WD review
- Confirm correct drape reference
- Camera Settings Review

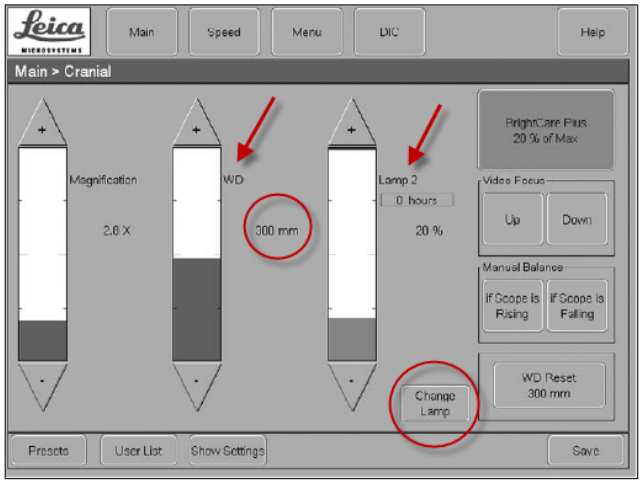


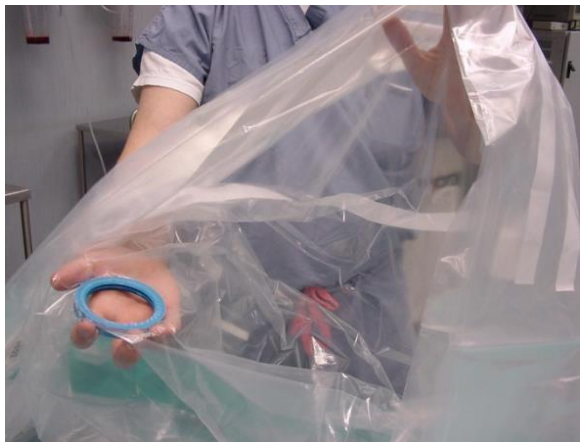






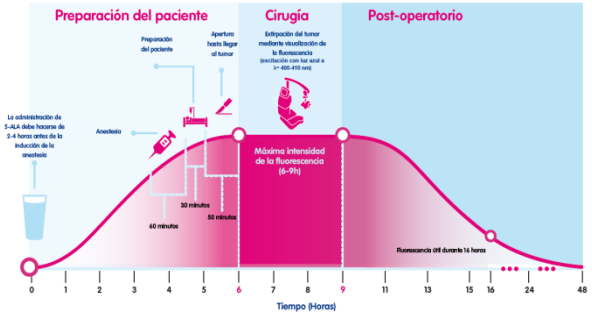


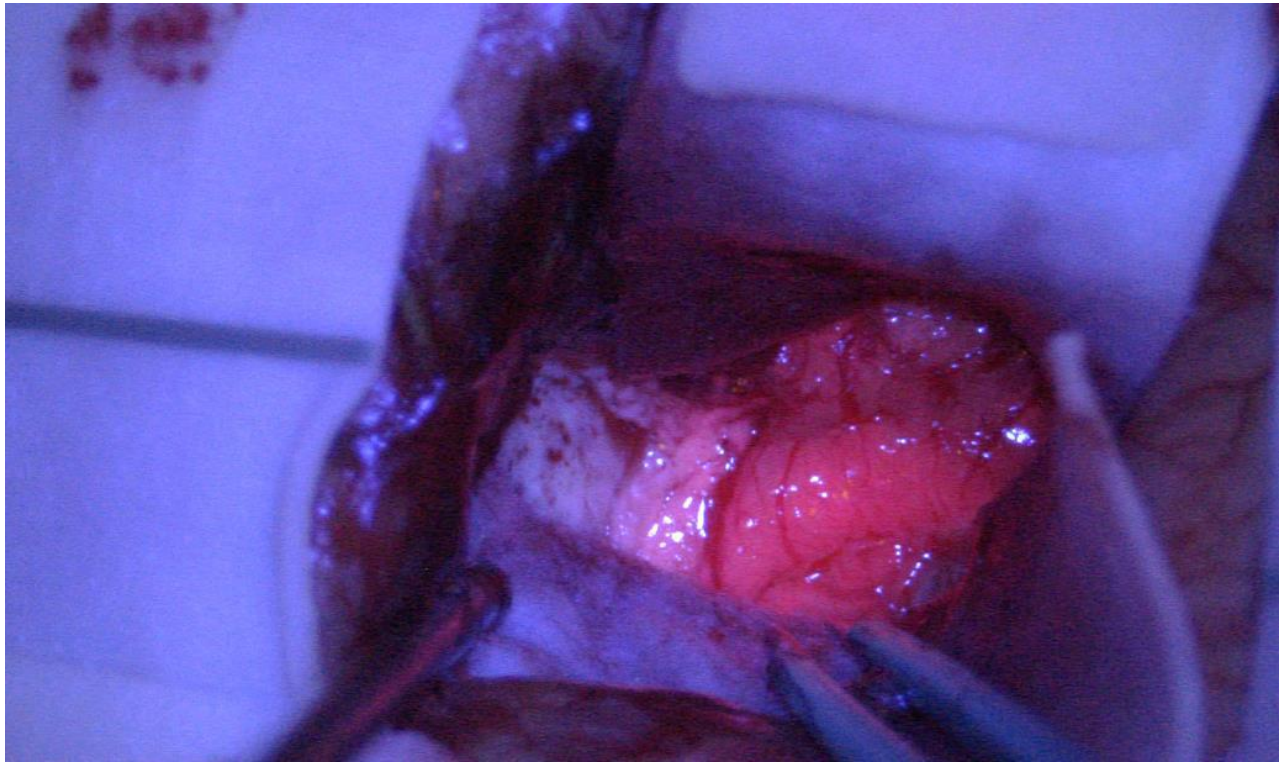




M530OH6 / M530OHX

- Review Administration Protocol
- Lamp Life Review

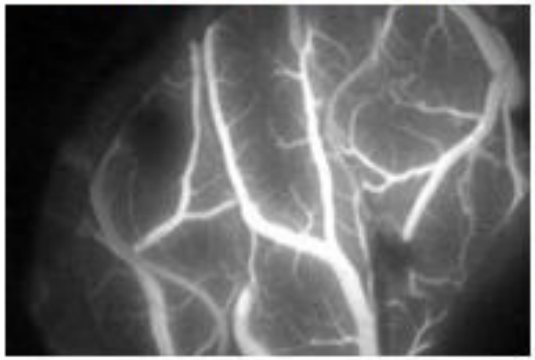




Best Microscope Ever created

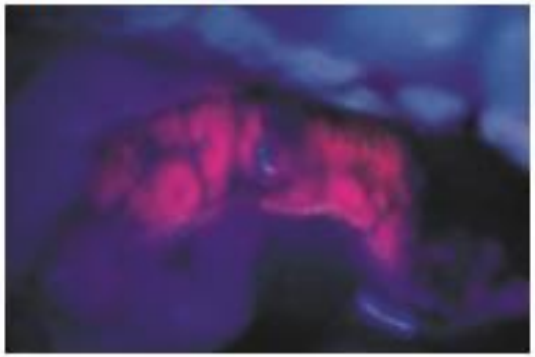
1- Best light power Xenon Bulbs 400W
2- Best Optics ever designed with high light transfer
3- No need to worry anymore about focus or camara rotation
4- Excellent team support
5- Unique Trifluorescence
6- Real Time surgeon position information on Optics Carrier
7- Improved Stand features and stability

Vascular Fluorescence



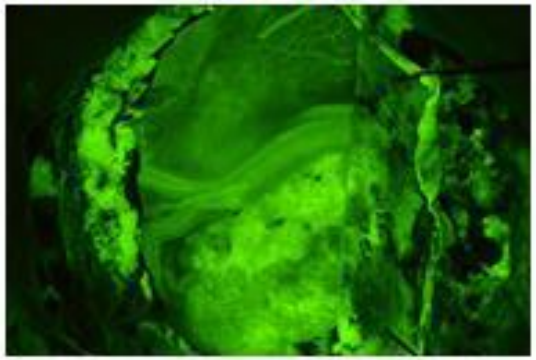
Leica FL800 intraoperative vascular fluorescence with ICG fluorescent agent.

Oncological Fluorescence



Leica FL400 intraoperative tumor fluorescence in conjunction with 5-ALA fluorescent agent.

Investigational Fluorescence



Leica FL560 fluorescence to observe fluorophores with an excitation peak from 460-500 nm (blue) and >510 nm.

Controversie (LGG)

- Storia naturale
- Fattori prognostici “tumor-related”
- Presenza di aspetti predittivi
- Impatto delle strategie terapeutiche
- **Ruolo del trattamento chirurgico**
- Ruolo della radioterapia precoce vs. ritardata
- Ruolo della chemioterpia

Low Grade Gliomas (LGG)

- Classe eterogenea (WHO I-II)
- Generalmente ci si riferisce all'astrocitoma diffuso (LGA), all'oligodendroglioma (ODG) ed al glioma misto (OA)…
- …ma includono anche l'ependimoma, lo xantoastrocitoma pleomorfo, l'astrocitoma subependimario a cellule giganti ed il ganglioglioma

Low Grade Gliomas (LGG)

- Percentuale
  - 55.5% maligni
  - 12.9% LGA
  - 7.7% ODG e OA
  - 18.9% senza diagnosi specifica

- Incidenza:
  - 2.38/100000/anno Maligni
  - 0.54/100000/anno LGA
  - 0.35/100000/anno OA

Low Grade Gliomas (LGG)

- Istologicamente sono classificati secondo due sistemi principali: St. Anne/Mayo(+/-) o WHO (+++)
- Negli anni le diagnosi di ODG sono aumentate a dispetto di quelle di LGA *(analisi citogenetica !)*
- Significativa differenza nella prognosi e trattamento *(Pignatti F, 2002 – Peraud A, 2002)*
- Sono in aumento anche le diagnosi di forme “overlap” (OA)

Sopravvivenza LGG sopratentoriali negli adulti

tipo istologico

sopravvivenza	Astro (LGA)	Oligo-astro (OA)	Oligo (OG)
mediana (yrs)	4.7	7.1	9.8
2 yrs (%)	80	89	93
5 yrs (%)	46	63	73
10 yrs (%)	17	33	49

(Shaw E, 1999)

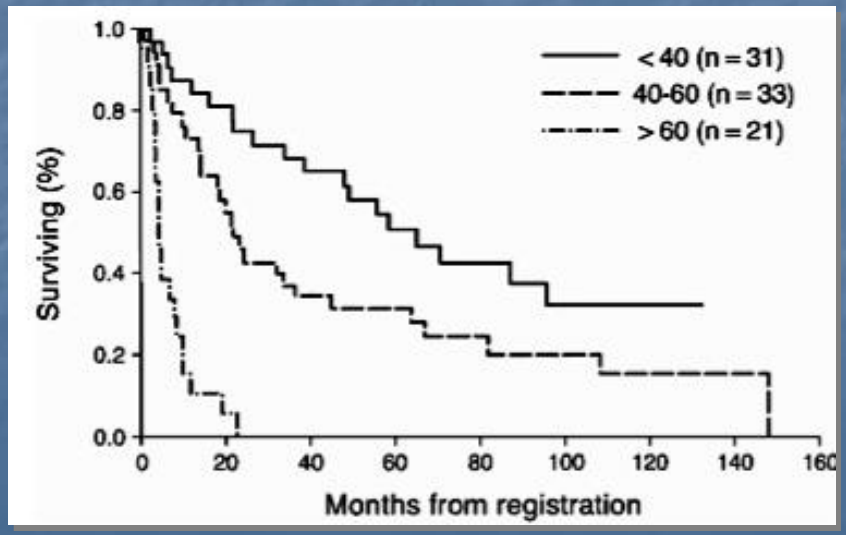
Storia naturale (LGG)

- Malattia cronica, invariabilmente fatale
- Eccezionalmente “lenta” in alcuni pazienti
- Timing delle terapie importante
  - *Comportamento “poco aggressivo”*
  - *Rischio di potenziale tossicità (lunga sopravvivenza)*
  - *Scopo palliativo*
- **Rimozione radicale curativa ?**

• E' ormai noto che i LGG sono lesioni dinamiche che durante la loro storia evolvono da un grado più basso di malignità ad uno maggiore.

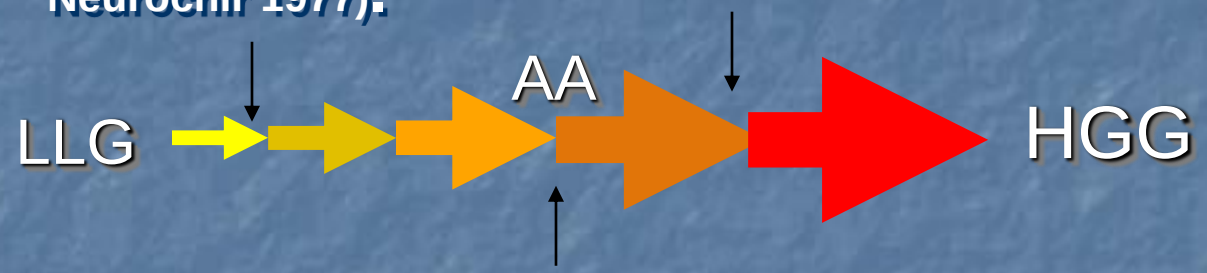
• Infatti pazienti più anziani al momento della diagnosi hanno una peggiore correlazione con l'intervallo verso la progressione (TTP) *(Shafqat S et al. Neurology 1999; Rasheed A, Cancer 2002)*

• Storie cliniche più brevi correlano con outcome peggiori *(Afra D. British J Neurosurg 1999)*



Perry, Cancer 1999

- In una serie di LGA recidivi il 14% presentava le stesse caratterisitche istologiche, 55% erano evoluti verso anaplastico ed il 30% erano GBM (Muller W et al. Acta Neurochir 1977).



mediana trasformazione: 7-8 anni, sopravvivenza 9-10 anni

- Quindi 2/3 progrediscono: fattori di rischio ?

Independent Genetic Pathways Leading to Glioblastoma

p53 mutations , 60%,
LOH 17p
PDGFR overexpression
telomerase activity, 20%

Astrocytoma II

LOH 19q
Rb alteration
telomerase activity, 40%

Astrocytoma III

LOH 10q
DCC loss expr, 50%
PDGFR amplification, <10%
telomerase activity, 100%

Secondary Glioblastoma

EGFR amplification 40%
p16/p14 deletion 40%

LOH 10p&q
PTEN mutations 30%

telomerase activity, 60%

Primary Glioblastoma

Ref. Kleihues et *al.* 1999, Hiraga et *al.* 1998, Cairncross et *al.* 1998

MOH 1.2002

Prognostic Factors for Survival in Adult Patients With Cerebral Low-Grade Glioma

By Francesco Pignatti, Martin van den Bent, Desmond Curran, Channa Debruyne, Richard Sylvester, Patrick Therasse, Denes Áfra, Philippe Cornu, Michel Bolla, Charles Vecht, and Abul B.M.F. Karim for the European Organization for Research and Treatment of Cancer Brain Tumor Cooperative Group and Radiotherapy Cooperative Group

J Clin Oncol 20:2076-2084. © *2002 by American Society of Clinical Oncology.*

LGG: fattori di rischio

- **Età ≥ 40**
- **Max ø ≥ 6 cm.**
- **Deficit neurologici (± crisi comiziali)**
- **Astrocitoma vs oligo/misto**
- **Non valutabile la presenza di "contrast enhancement" (40%)**
- ***Estensione della chirurgia non significativa***
- **Scoring system *(non validato in trials clinici !!):***

  ≤ 2 fattori di rischio → ST > 7 yrs

  ≥ 3 fattori di rischio → ↓↓↓ ST

Acta Neurochir (Wien) (1998) 140: 1213–1222

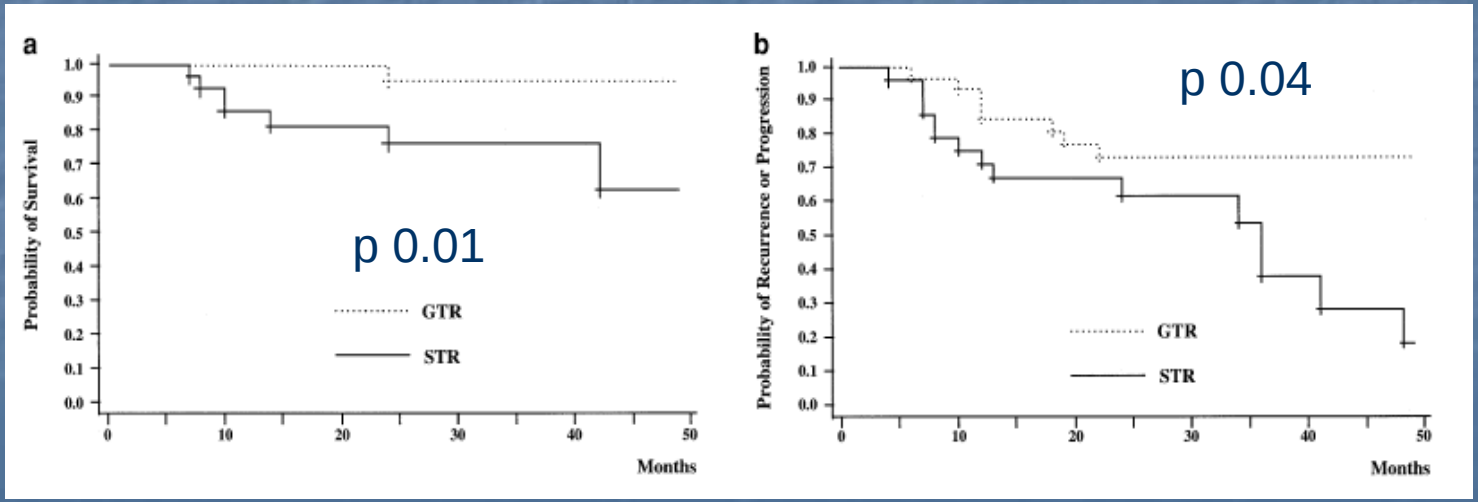
Acta Neurochirurgica

Clinical Outcome of Supratentorial Astrocytoma WHO Grade II

A. Peraud[1], H. Ansari[3], K. Bise[2], and H.-J. Reulen[1]

75 pts

Median FU 24 mo



OS

TTP

Vol. 8, 1117–1124, May 2002 Clinical Cancer Research **1117**

Prognostic Impact of *TP53* Mutations and P53 Protein Overexpression in Supratentorial WHO Grade II Astrocytomas and Oligoastrocytomas[1]

Aurelia Peraud,[2] Friedrich W. Kreth, Otmar D. Wiestler, Paul Kleihues, and Hans-Jürgen Reulen

159 pts

Median FU 49.1± 36.6 mo

Prognostic Factors and Length of Survival. The prognostic impact of variables was tested in several alternative models, which did not contain more than four variables (because of the low number of events). The only unfavorable predictor for length of survival was increasing age (≥40 years) after univariate and multivariate analysis ($P < 0.05$; risk ratio, 2.3; 95% confidence interval, 1.1–4.9). Nonsignificant variables were KPS, sex, seizures at the time of presentation, histological subtype, *TP53* mutational status, and treatment related factors (EOR and radiation therapy). No prognostic factor could be identified for postrecurrence survival. The same prognostic pattern was obtained for 129 patients with *de novo* tumors (data not shown).

Finalità della chirurgia

- Definizione di una diagnosi biopatologica
  - ***Biopsia stereotassica***
- Ridurre l'effetto massa
- Migliorare il quadro neurologico
- Valore prognostico dell'estensione della chirurgia
- Confermare l'istotipo e il grado al momento della progressione
- Sempre indicata al momento della diagnosi ??

Indicazioni al trattamento chirurgico

- **Timing del trattamento chirurgico controverso *(no studi prospettici !!)***
- **Lesioni con effetto massa e deterioramento neurologico rappresentano una chiara indicazione alla rimozione chirurgica**
- **Lesioni prive di effetto massa, infiltranti, senza deficit neurologici, rappresentano ancora una *scelta difficile ed aperta***

Indicazioni al trattamento chirurgico (1)

- "*Primum non nocere*": la politica del "wait and see" può essere indicata in pz. giovani, con epilessia cronica ben controllata, con lesioni di piccolo volume in aree critiche, senza effetto massa e/o contrast enhancement

- La resezione precoce di tumori potenzialmente curabili è preferibile, ma molti Autori non riportano prognosi più sfavorevoli, in caso di chirurgia ritardata in pazienti paucisintomatici

Indicazioni al trattamento chirurgico (2)

- **Rischi potenziali connessi alla chirurgia ritardata:**
  - ***Progressione tumorale maligna***
  - ***Deficit neurologici irreversibili***
  - ***Epilessia più diffusa e resistente***

- **È ben definito il ruolo della chirurgia precoce nel controllo delle crisi e della potenziale diffusione dell'attività elettrica interictale**

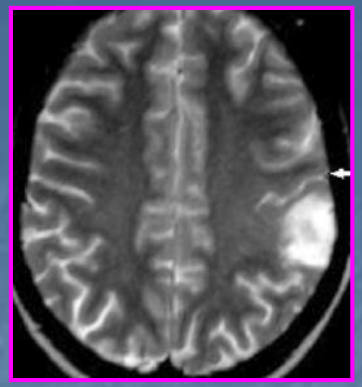
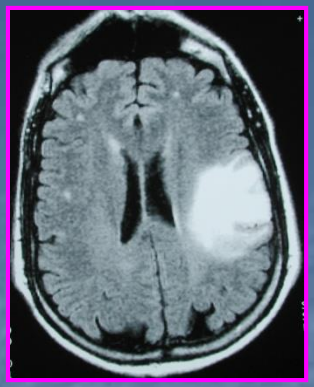
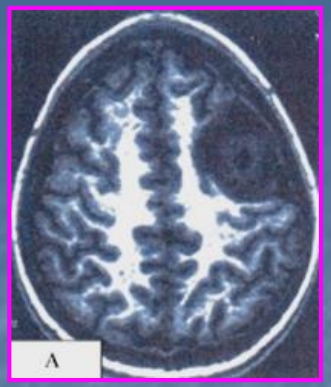
Estensione della chirurgia

- I dati della letteratura non sono univoci circa il rapporto tra l'entità della rimozione chirurgica e la sopravvivenza (OS)
- L'interpretazione dei dati è complicata dalla selezione di pazienti, qualità degli studi (serie retrospettive), soggettiva valutazione dell'entità della rimozione
- Il miglioramento delle tecniche chirurgiche ha sicuramente influenzato un atteggiamento più aggressivo, con lo scopo di una rimozione radicale e minima morbidità neurologica

Specificità LGG

- Età: LGA 30-34 anni
  ODG 45-49

- **Localizzazione:** **82.6% in aree critiche**
  - 27.3% regione precentrale frontomesiale (SMA)
  - 25% invasione dell'insula con o senza invasione della corteccia fronto-orbitale o temporo-polare (così detto sistema paralimbico)
  - 18.9% centri del linguaggio (area premotrice/Broca; area temporale posteriore sinistra; giunzione parieto-temporale)
  - 6% area sensori-motoria primaria
  - 4.5% area motoria primaria
  - 0.75% area visiva primaria


Scenario tipico

- Spesso **ASINTOMATICO** e **GIOVANE**
- **EPILESSIA** ben controllata
- **Localizazione in aree eloquenti**

Chi trattare, quando e come?

- **Allo stato attuale non esiste alcuna evidenza statistica della superiorità (SOPRAVVIVENZA!!) di un trattamento su di un altro**
    - **Biopsia**
    - **Chirurgia**
    - **RT**
    - **CT**

- **Allo stesso modo è però sempre più chiaro che il "wait and see" può indurre a sottostimare l'efficacia delle terapie sul tumore**

- **In tutti i casi prima di qualsiasi scelta terapeutica è NECCESSARIO ottenere quanti più dati possibili: *clinici, neuroradiologici, biologici***

1. Clinici

- Età al momento della diagnosi *(EORTC 22844, 2002)*
- Valutazione neuropsicologica:
  - *NON BASTA IL MINGAZZINI!!!*
  - *Tumori più sintomatici possono rappresentare espressione di aggressività*
  - *Variazioni del quadro possono corrispondere ad evoluzione*
  - *Eventuale programmazione dei test intraoperatori*
  - *Strutturazione della riabilitazione postoperatoria*
- Attento follow-up delle crisi epilettiche (Francavilla TL, Neurosurgery 1989)

2. Neuroradiologici

•Valutare sempre T1 con mdc, T2, FLAIR: nei LGG tutto l'ipersegnale è tumore e MAI edema

•Comparsa di "contrast enhancement"

•Calcolare i diametri maggiori sui 3 piani e arrotondare un volume (X x Y x Z/2)

•Ottenere sempre una serie di controlli RM prima di ogni scelta e valutare le curve di crescita

•Un aumento del diametro da 3 a 3.4 cm corrisponde ad un aumento di volume del 45% (a 3.8 cm = 100%)

•Mandonnet et al (Annals of Neurology 2003) hanno dimostrato (in un subset di LGG non candidati alla resezione chirurgica) che i LGG hanno un pattern di crescita lineare:

mediamente 4.1 mm per anno

(Swanson KR 2000, Cell Prolif; Woodward DE 1996, Cell Prolif)

2. Neuroradiologici

- La SpettroRM e la DWI/Perfusion possono fornire molte informazioni affidabili sul grado di differenziazione del tumore

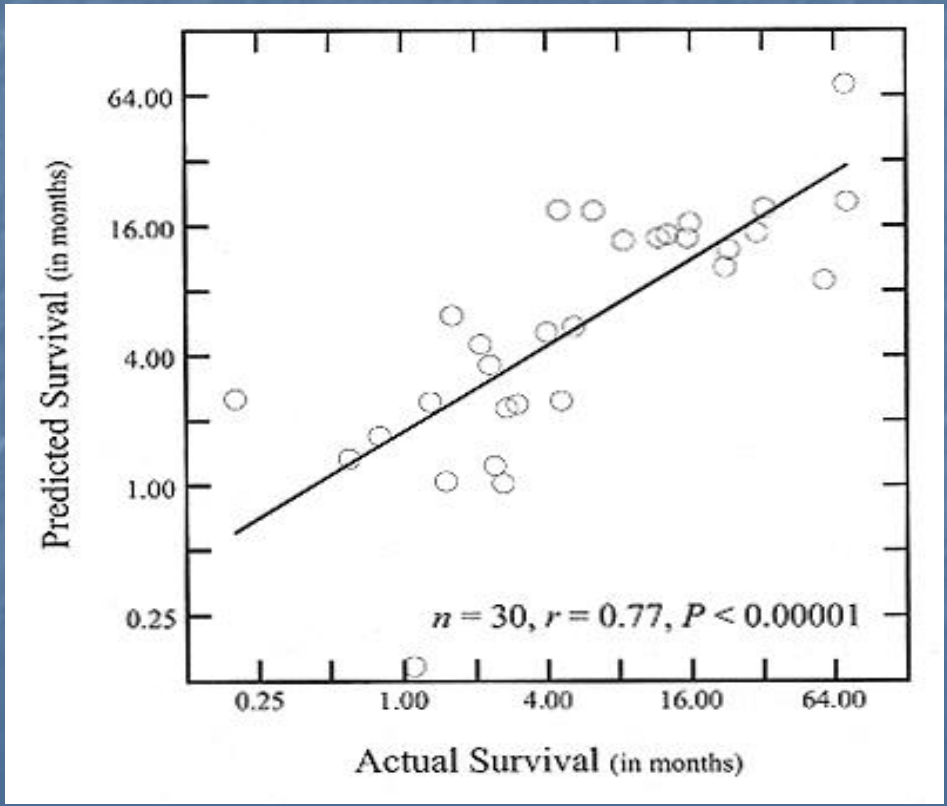
- analizzano la totalità della lesione (a differenza di una biopsia)

- possono guidare la biopsia

- Il rCBV si è dimostrato efficace nel rilevare tumori di alto grado “sfuggiti” alle metodiche classiche e cogliere precocemente l’evoluzione maligna (Law et al, Neurosurgery 2006)

Proton Magnetic Resonance Spectroscopic Imaging Can Predict Length of Survival in Patients with Supratentorial Gliomas

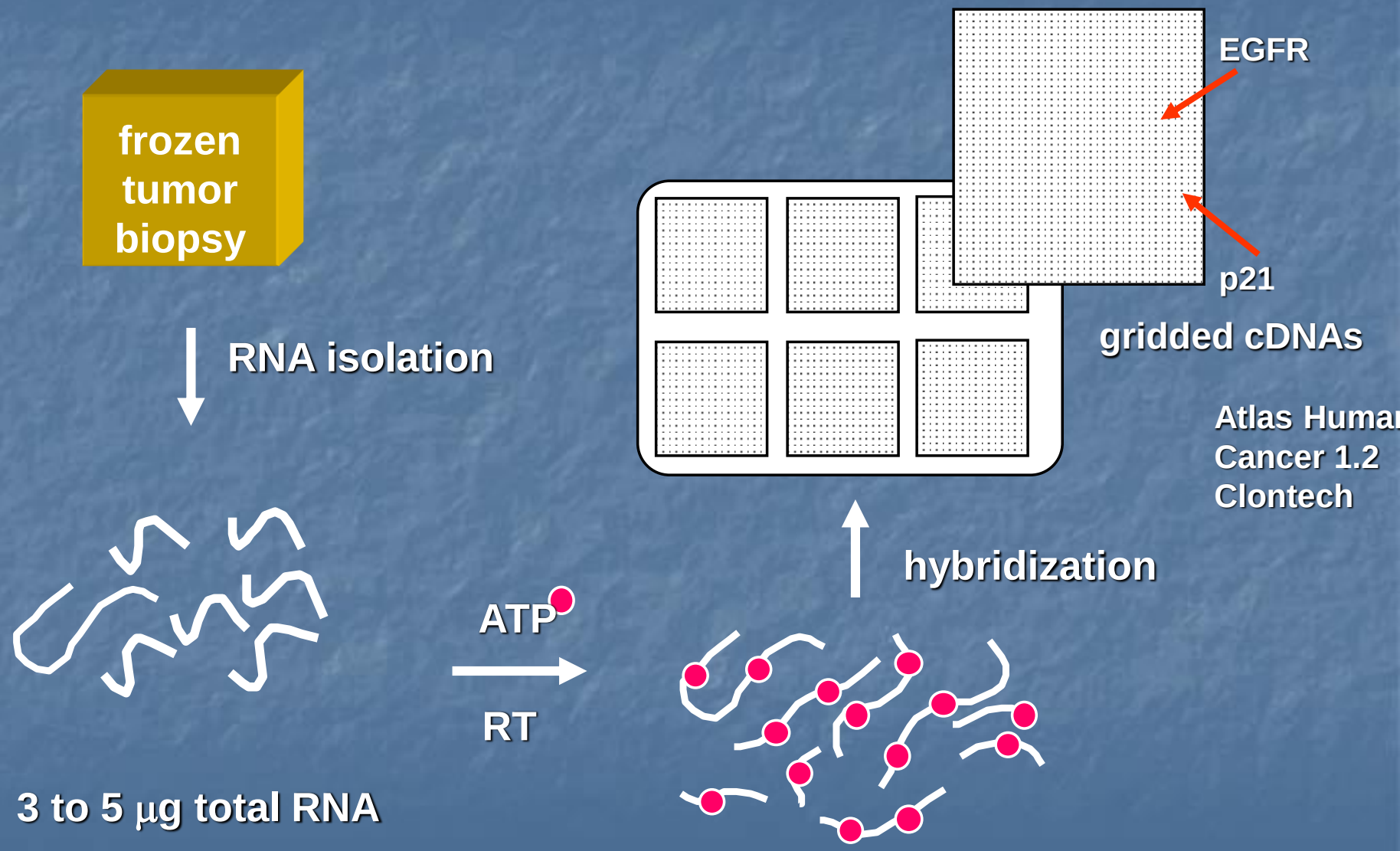
Neurosurgery 53:565-576, 2003 DOI: 10.1227/01.NEU.0000079331.21178.8E



3. Biologici

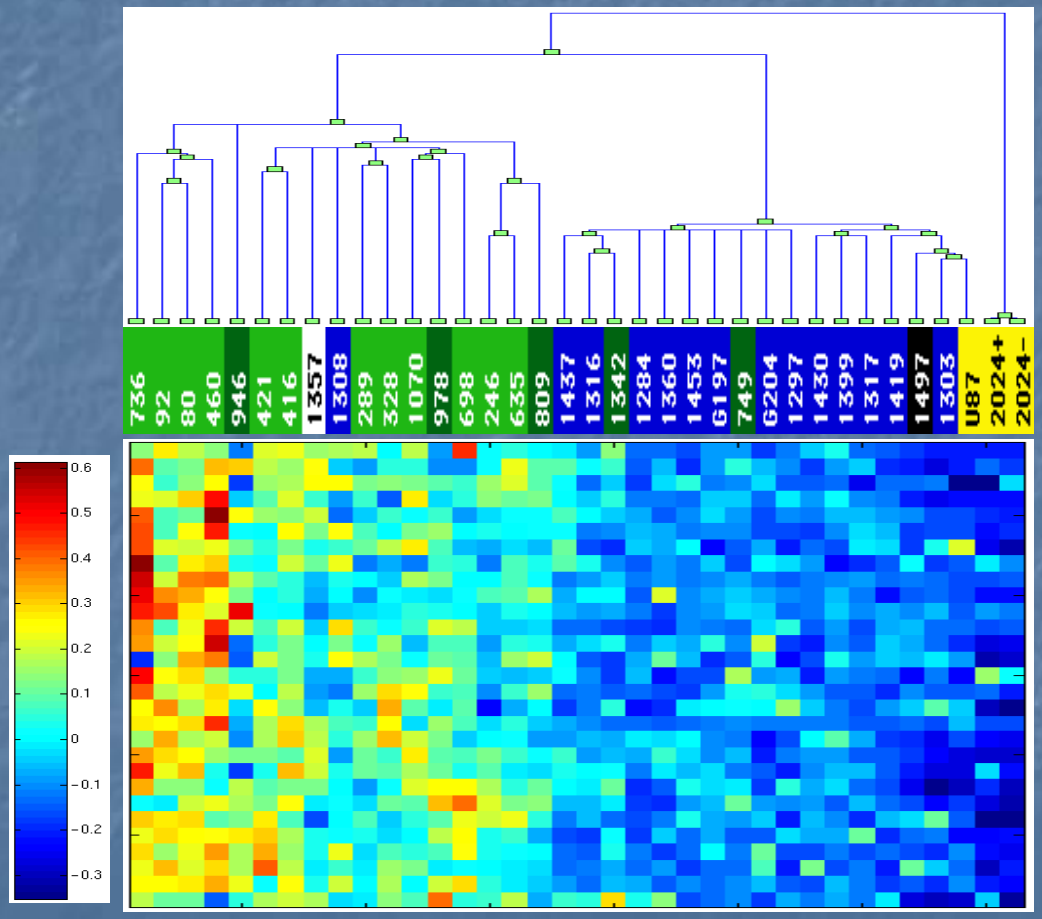
- La progressione avviene per accumulo di alterazioni genetiche
  (Walker DG. Molecular genetics of astrocytoma: a review. J Clin Neurosci 1997)
- Ottenere sempre un esame istologico e citogenetico anche nei casi non canditati all'exeresi
- Individuare quanti più indici possibile per rilevare precocemente un viraggio

Gene Expression Analysis on cDNA-Arrays



Super-Paramagnetic Clustering of 36 Experiments by Genes of Node505

Node 505 was identified as rich in genes separating glioblastomas from low grade astrocytomas as determined by supervised analysis



Low grade astrocytoma
Secondary GBM
Primary GBM
Glioma cell line

Node 505

X98085 tenascin-R
X59656 CRK-like protein
U12140 BDNF/NT-3 growth factors receptor precursor
Y11044 GABA-B receptor 1A subunit (GABA-BR1A)
L42373 protein phosphatase 2A B56-alpha
Y08110 low-density lipoprotein receptor-related protein LR11 precursor

M99437 neurogenic locus notch protein (N)
M27968 heparin-binding growth factor 2 precursor (HBGF2; bFGF; FGF2)

X16841 NCAM120; CD56 antigen
X87838 beta catenin (CTNNB)
M32865 Ku 70-kDa subunit
U33286 cellular apoptosis susceptibility protein (CAS)
D84476 mitogen-activated protein kinase kinase kinase 5 (MAPKKK5; MEKK5

X03663 macrophage colony stimulating factor I receptor precursor (CSF-1-R)

U69126 fuse-binding protein 2 (FBP2)
D50477 MMP16
M27364 elongation factor 1 alpha (EF1 alpha)
D17516 pituitary adenylate cyclase activating polypeptide I receptor precursor

Y08263 AAD14 protein
AB007867 KIAA0407
X76104 death-associated protein kinase 1 (DAP kinase 1; DAPK1)

X97335 dual-specificty A-kinase anchoring protein 1
U60062 zygini; FEZ1-T
X74295 integrin alpha 7B precursor (IGA7B)
X95456 Rho7 protein
U37122 adducin gamma subunit
D63878 NEDD5 protein homolog; DIFF6; KIAA0158
U9091 clone 23815 (Soares library 1NIB from IMAGE Consortium)

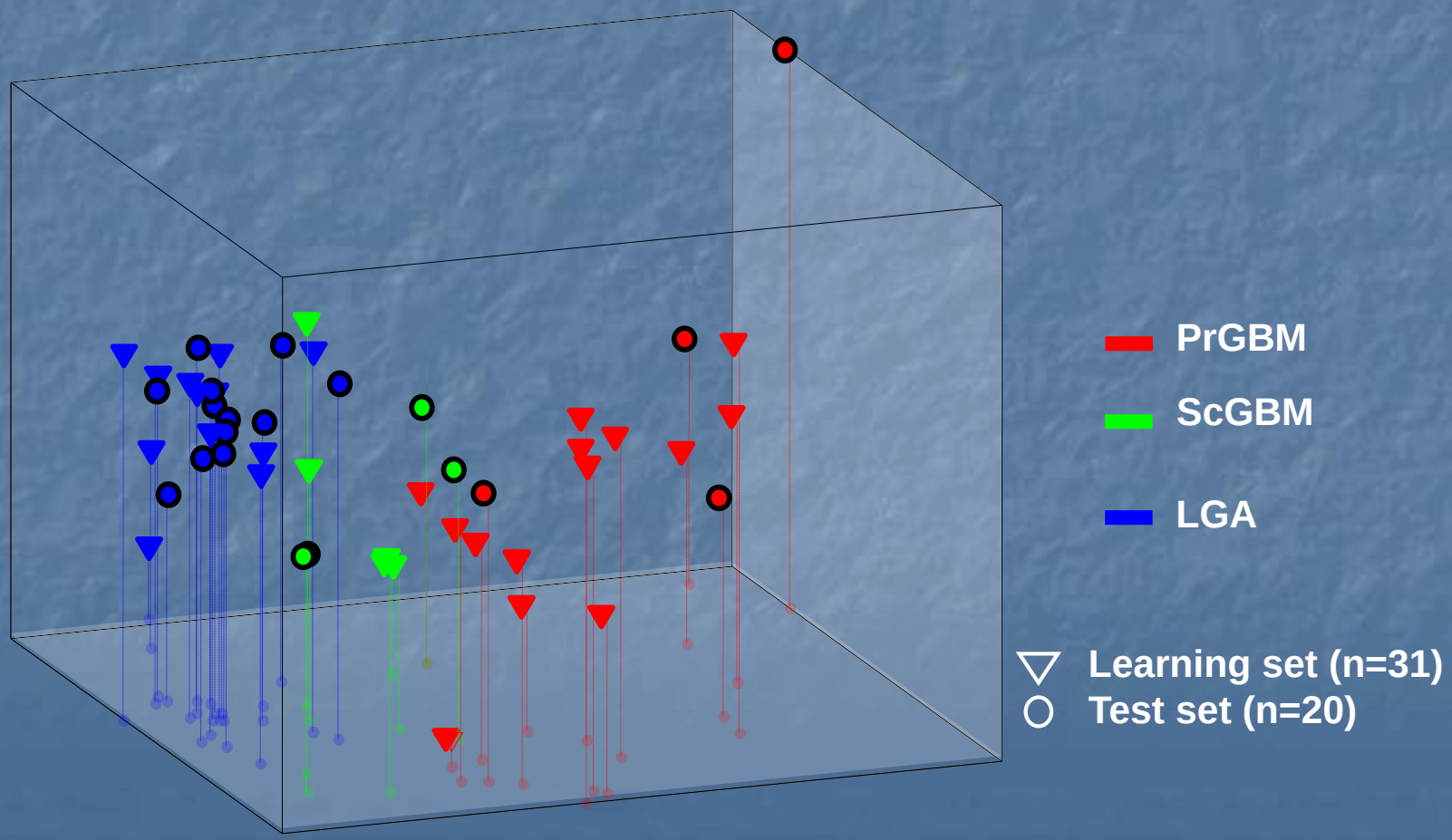
U72649 btg protein precursor; NGF-inducible anti-proliferative protein PC3

[CANCER RESEARCH 63, 6613–6625, October 15, 2003]

Classification of Human Astrocytic Gliomas on the Basis of Gene Expression: A Correlated Group of Genes with Angiogenic Activity Emerges As a Strong Predictor of Subtypes[1,2]

Sophie Godard, Gad Getz, Mauro Delorenzi, Pierre Farmer, Hiroyuki Kobayashi, Isabelle Desbaillets, Michimasa Nozaki, Annie-Claire Diserens, Marie-France Hamou, Pierre-Yves Dietrich, Luca Regli, Robert C. Janzer, Philipp Bucher, Roger Stupp, Nicolas de Tribolet, Eytan Domany, and Monika E. Hegi[3]

MDS (multidimensional scaling) of 1185 genes and 51 astrocytic gliomas



Ruolo della chirurgia di exeresi

•Il volume tumorale al tempo della diagnosi così come tumori che sorpassano la linea mediana sono fattori negativi sia di Overall Survival (OS) che di Progression Free Survival (PFS). (Karim AB. EORTC 22844, 1996; Shaw E et al NCCTG, 2002)

• Il volume iniziale del tumore influenzerebbe il viraggio. Come dire « più cellule, più rischio di progressione ».

•Berger et al. hanno dimostrato che i pazienti più a rischio di progressione tumorale e/o recidiva erano quelli con la massa tumorale iniziale più voluminosa e con il residuo post-chirurgico maggiore (≥ 10 cm^3) (Cancer 1994)

•Sebbene gravati dai limiti di disegno, **la maggior parte dei lavori indica l'asportazione macrosopicamente totale come un fattore di aumentata sopravvivenza rispetto alla resezione parziale.** (Keles et al. J N S 2001; Kaye AH. J Clin Neurosci 2000)

See the Editorial and the Response in this issue, pp 731–732.

J Neurosurg 95:735–745, 2001

Low-grade hemispheric gliomas in adults: a critical review of extent of resection as a factor influencing outcome

G. Evren Keles, M.D., Kathleen R. Lamborn, Ph.D., and Mitchel S. Berger, M.D.

Department of Neurological Surgery, Brain Tumor Research Center, University of California at San Francisco, California

TABLE 1

*Studies in which the prognostic effect of extent of resection on survival was assessed using statistical analysis**

TABLE 4

*Selected studies in which the prognostic effect of extent of resection on outcome was assessed using statistical analysis**

Authors & Year	Years of Study	No. of Patients	Groups	No. of Patients	5-Year PFS Rate (%)	5-Year S Rate (%)	10-Year S Rate (%)	MST (yrs)	UV p Value	MV p Value
Soffietti, et al., 1989	1950–1982	81†	GTR	19	NA	51	11	5	<0.001	<0.01
			STR	49	NA	24	3	3.3		
			PR	13	NA	0	0	1.6		
Philippon, et al., 1993	1978–1987	179	GTR	45	NA	80	NA	NA	0.0002	<0.01
			STR	95	NA	50	NA	NA		
			Bx	39	NA	45	NA	NA		
Rajan, et al., 1993	1974–1990	82	GTR	11	NA	90	68	NA	<0.05	NS
			STR	30	NA	52	36	NA		
			PR	22	NA	50	31	NA		
			Bx	19	NA	42	28	NA		
Leighton, et al., 1997	1979–1995	167	min RD	82	NA	82	59	10.7	0.008	0.006
			bulky RD	85	NA	64	41	8.4		
van Veelen, et al., 1998	1975–1989	90	>75% res	13	46	62	NA	NA	0.002	0.04
			<75% res	59	10	18	NA	NA		
			Bx	18	28	33	NA	NA		

* Studies in which the population exceeded 75 patients, excluding pediatric patients and those with pilocytic or gemistocytic tumors.
Abbreviations: MST = median survival time; PFS = progression-free survival; res = resection; S = survival.
† In this study 81 of 85 cases (Table 1) were analyzed.

See the Editorial and the Response in this issue, pp 731–732.

J Neurosurg 95:735–745, 2001

Low-grade hemispheric gliomas in adults: a critical review of extent of resection as a factor influencing outcome

G. Evren Keles, M.D., Kathleen R. Lamborn, Ph.D., and Mitchel S. Berger, M.D.

Department of Neurological Surgery, Brain Tumor Research Center, University of California at San Francisco, California

TABLE 4

*Selected studies in which the prognostic effect of extent of resection on outcome was assessed using statistical analysis**

Authors & Year	Years of Study	No. of Patients	Groups	No. of Patients	5-Year PFS Rate (%)	5-Year S Rate (%)	10-Year S Rate (%)	MST (yrs)	UV p Value	MV p Value
Soffietti, et al., 1989	1950–1982	81†	GTR	19	NA	51	11	5	<0.001	<0.01
			STR	49	NA	24	3	3.3		
			PR	13	NA	0	0	1.6		
Philippon, et al., 1993	1978–1987	179	GTR	45	NA	80	NA	NA	0.0002	<0.01
			STR	95	NA	50	NA	NA		
			Bx	39	NA	45	NA	NA		
Rajan, et al., 1993	1974–1990	82	GTR	11	NA	90	68	NA	<0.05	NS
			STR	30	NA	52	36	NA		
			PR	22	NA	50	31	NA		
			Bx	19	NA	42	28	NA		
Leighton, et al., 1997	1979–1995	167	min RD	82	NA	82	59	10.7	0.008	0.006
			bulky RD	85	NA	64	41	8.4		
van Veelen, et al., 1998	1975–1989	90	>75% res	13	46	62	NA	NA	0.002	0.04
			<75% res	59	10	18	NA	NA		
			Bx	18	28	33	NA	NA		

* Studies in which the population exceeded 75 patients, excluding pediatric patients and those with pilocytic or gemistocytic tumors.
Abbreviations: MST = median survival time; PFS = progression-free survival; res = resection; S = survival.
† In this study 81 of 85 cases (Table 1) were analyzed.

Contribution of intraoperative electrical stimulations in surgery of low grade gliomas: a comparative study between two series without (1985–96) and with (1996–2003) functional mapping in the same institution

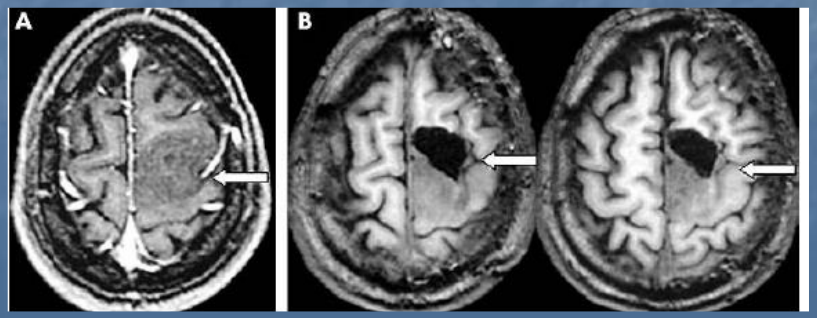
H Duffau, M Lopes, F Arthuis, A Bitar, J-P Sichez, R Van Effenterre, L Capelle

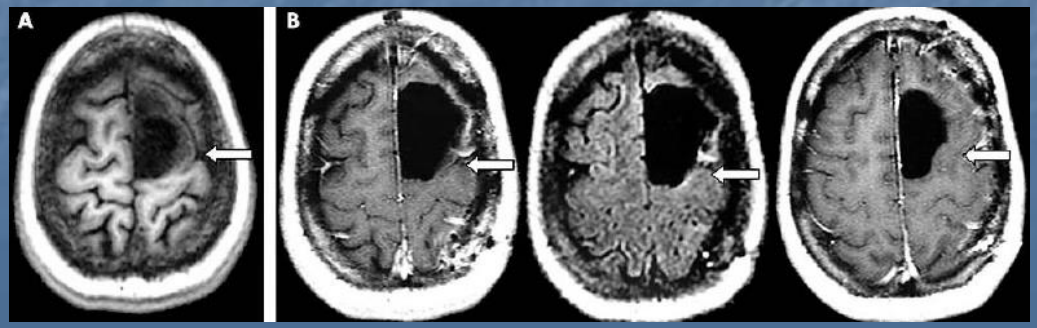
J Neurol Neurosurg Psychiatry 2005;**76**:845–851. doi: 10.1136/jnnp.2004.048520

62% di LGG operati in area critica vs 35%

6.5% sequele definitive vs 17% (nonostante sedi più critiche)

25.4% resezioni totali (RM) vs 6%





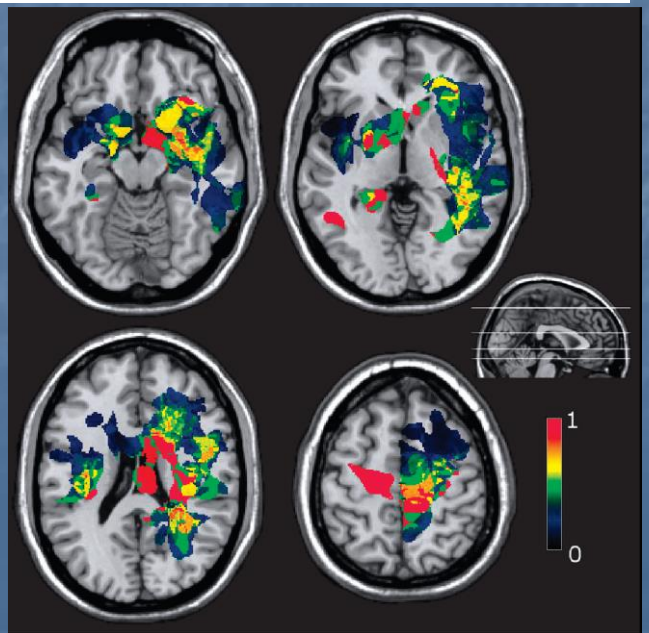
NEURO-ONCOLOGY

Preoperative estimation of residual volume for WHO grade II glioma resected with intraoperative functional mapping

Emmanuel Mandonnet, Saad Jbabdi, Luc Taillandier, Damien Galanaud, Habib Benali, Laurent Capelle, and Hugues Duffau[1]

Departments of Neurosurgery (E.M., L.C., H.D.) and Neuroradiology (D.G.), Hôpital de la Pitié-Salpêtrière, 75651 Paris; UMR-S678 Institut National de la Santé et de la Recherche Médicale (E.M., S.J., L.C., H.B., H.D.), 75654 Paris; and Department of Neurology, Centre Hospitalier Universitaire Nancy, 54000 Nancy (L.T.); France

Se volume residuo post-chirurgia stimabile > 10 cm^3 , chirurgia utile ??



CORRELAZIONE TRA PERCENTUALE DI RESEZIONE E SOPRAVVIVENZ

TABLE 1: Results of a multivariate Cox proportional hazards analysis to assess effect of EOR on survival in patients with GBM*

Variable	HR (95% CI)	p Value
age	1.01 (1.01–1.02)	<0.0001
KPS score	0.99 (0.98–0.99)	0.001
EOR	0.99 (0.98–0.99)	0.004
log (postop tumor vol +1)	1.07 (1.04–1.11)	<0.0001

* This final analysis designated age ($p < 0.0001$), KPS score ($p = 0.001$), EOR ($p = 0.004$), and postoperative tumor volume ($p < 0.0001$) as predictors of overall survival in patients with GBM.

Surgeon independant variable

Can be influeced by surgery

J Neurosurg 115:3–8, 2011

NADER SANAI, M.D.,[1] MEI-YIN POLLEY, PH.D.,[2] MICHAEL W. MCDERMOTT, M.D.,[1] ANDREW T. PARSA, M.D., PH.D.,[1] AND MITCHEL S. BERGER, M.D.[1]

[1]*Brain Tumor Research Center, and* [2]*Division of Biostatistics, Department of Neurological Surgery, University of California, San Francisco, California*

LA % DI RESEZIONE INFLUENZA LA SOPRAVVIVEZA

Criticità:

Valutazione del chirurgo e possibilità di resezione

La sede del tumore influenza sicuramente l'estensione della resezione (EOR)

L'EOR dipende dall'abilità del chirurgo di giudicare la presenza di tumore residuo durante la chirurgia.

Generalmente l'abilità del chirurgo di giudicare la completezza della resezione è inaccurata
(sembra che vicino alle aree più 'pericolose' la sovrastima dell'EOR sia maggiore)

J Neurosurg 117:851–859, 2012

Extent of resection in patients with glioblastoma: limiting factors, perception of resectability, and effect on survival

Clinical article

*Daniel Orringer, M.D.,[1] Darryl Lau, B.A.,[2] Sameer Khatri, B.S.,[2]
Grettel J. Zamora-Berridi, M.H.S.,[2] Kathy Zhang, B.A.,[2] Chris Wu, B.S.,[2]
Neeraj Chaudhary, M.B.B.S., M.R.C.S., F.R.C.R.,[3] and Oren Sagher, M.D.[1]

Departments of [1]Neurosurgery and [3]Radiology, University of Michigan; and [2]University of Michigan Medical School, Ann Arbor, Michigan

QUALI SONO LE SEDI CRITICHE

CALLOSO

Tanti gli articoli sulla via transcallosa o sulla callosotomia per epilessia

J Neurosurg Pediatrics 7:98–103, 2011

Transcallosal interforniceal approach to pineal region tumors in 150 children

Clinical article

Wenqing Jia, M.D.,[1] Zhenyu Ma, M.D.,[1] Isabelle Yisha Liu, M.D.,[2] Yuqi Zhang, M.D.,[1] Ge Jia, M.D.,[1] and Weiqing Wan, M.D.[1]

[1]Department of Neurosurgery, TianTan Hospital, Capital University of Medical Science, Beijing, China; and [2]Washington University in St. Louis, School of Medicine, St. Louis, Missouri

Seizure 21 (2012) 307–309

Contents lists available at SciVerse ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Case report

Corpus callosotomy for treatment of pediatric refractory status epilepticus

Hansel M. Greiner[a,*], Jan-Mendelt Tillema[b], Barbara E. Hallinan[a], Katherine Holland[a], Ki-Hyeong Lee[c], Kerry R. Crone[d]

[a] Department of Pediatrics, Division of Child Neurology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH 45229, United States
[b] Department of Neurology, Division of Child Neurology, Mayo Clinic, Rochester, MN, United States
[c] Comprehensive Pediatric Epilepsy Center, Florida Hospital for Children, Orlando, FL, United States
[d] Division of Pediatric Neurosurgery, University of Cincinnati, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States

Ma pochi sulla chirurgia dei gliomi a livello del calloso

J Neurosurg 100:431–437, 2004

Surgical removal of corpus callosum infiltrated by low-grade glioma: functional outcome and oncological considerations

Hugues Duffau, M.D., Ph.D., Ihab Khalil, M.D., Peggy Gatignol, S.T., Dominique Denvil, M.D., and Laurent Capelle, M.D.

Departments of Neurosurgery and Neurology, Hôpital de la Salpêtrière, Paris, France

GANGLI DELLA BASE

Clinical Articles

Thalamic Astrocytomas: Surgical Anatomy and Results of a Pilot Series Using Maximum Microsurgical Removal

H.-J. Steiger, C. Götz, R. Schmid-Elsaesser, and **W. Stummer**

Department of Neurosurgery, Klinikum Grosshadern, Ludwig-Maximilians University Munich

Acta Neurochir (Wien) (2000) 142: 1327–1337

Age	Side	Tumor ∅	Histology	Approach and % removal	Postoperative complications	Events during follow-up	Follow-up time
4 ys	right	4.5 cm	pilocytic astrocytoma	transventricular 100%	–	–	52 months
6 ys	right	4 cm	anaplastic astrocytoma	infratentorial 80%	hydrocephalus, VP-shunt	–	16 months
25 ys	left	3.5 cm	astrocytoma II	transventricular 90%	partial hemianopia	–	10 months
54 ys	left	4 cm	glioblastoma	transventricular 70%	–	progression, death at 4 months	–
30 ys	right	5 cm	pilocytic astrocytoma	transventricular 90%	–	–	21 months
16 ys	left	3 cm	pilocytic astrocytoma	transventricular 100%	hydrocephalus, VP-shunt, transient disturbed consciousness	–	34 months
30 ys	left	5 cm	glioblastoma	transventricular 95%	partial hemianopia	–	6 months
48 ys	right	4 cm	anaplastic astrocytoma	transventricular 70%	–	progression, hydrocephalus, shunt	14 months
32 ys	right	3.5 cm	anaplastic astrocytoma	transventricular 70%	hydrocephalus, VP-shunt	progression	25 months
31 ys	right	2.5 cm	anaplastic astrocytoma	infratentorial 100%	hydrocephalus, VP-shunt	–	15 months
9 ys	left	5 cm	anaplastic astrocytoma	transventricular 95%	–	progression	16 months
64 ys	left	2 cm	anaplastic astrocytoma	infratentorial 100%	–	progression	10 months
10 ys	right	2 cm	anaplastic astrocytoma	infratentorial 100%	–	progression, hydrocephalus, death at 22 months	22 months
51 ys	right	5 cm	glioblastoma	transventricular 90%	–	–	10 months

INSULA

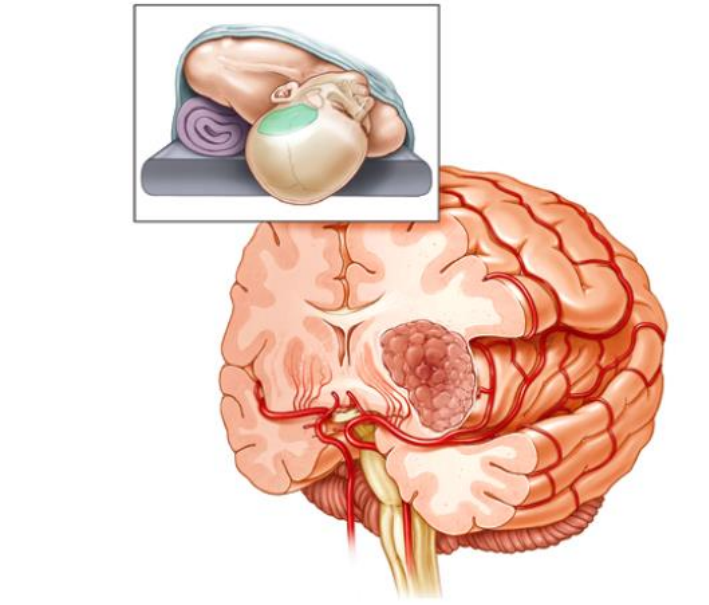
Resection of insular gliomas: the importance of lenticulostriate artery position

Clinical article

YARON A. MOSHEL, M.D., PH.D., JOSHUA D.S. MARCUS, B.A., ERIK C. PARKER, AND PATRICK J. KELLY, M.D.

Department of Neurosurgery, New York University School of Medicine, New York, New York

MENO FAVOREVO
PER RESEZIONE



EVOLE

Insular gliomas: the case for surgical management

Clinical article

MATTHIAS SIMON, M.D.,[1] GEORG NEULOH, M.D.,[1] MAREC VON LEHE, M.D.,[1] BERNHARD MEYER, M.D.,[2] AND JOHANNES SCHRAMM, M.D.[1]

[1]Neurochirurgische Klinik, Universitätskliniken Bonn; and [2]Neurochirurgische Klinik, Technische Universität München, Klinikum rechts der Isar, München, Germany

J Neurosurg 110:685–695, 2009

A favore della chirurgia per i gradi I-III
Cautela nei pazienti con età > 60 anni e
Con glioblastoma

AREA DEL LINGUAGGIO

Matthew J. McGirt, M.D.
Department of Neurosurgery,
The Neuro-Oncology Surgical
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Baltimore, Maryland

Debraj Mukherjee, M.D., M.P.H.
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Baltimore, Maryland

Kaisorn L. Chaichana, M.D.
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Outcomes Research Laboratory,
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Baltimore, Maryland

Khoi D. Than, M.D.
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University of Michigan School of Medicine,
Ann Arbor, Michigan

Jon D. Weingart, M.D.
Departments of Neurosurgery
and Oncology,
The Johns Hopkins University
School of Medicine,
Baltimore, Maryland

Alfredo Quinones-Hinojosa, M.D.

ASSOCIATION OF SURGICALLY ACQUIRED MOTOR AND LANGUAGE DEFICITS ON OVERALL SURVIVAL AFTER RESECTION OF GLIOBLASTOMA MULTIFORME

Lo sviluppo di nuovi deficit motori e del linguaggio nel postoperatorio
Si associava ad una sopravvivenza ridotta a parità di resezione e di
Trattamento, quindi non solo come già noto a ridotta qualità di vita!

Neurosurgery 65:463–470, 2009

AREA MOTORIA

Impact of Intraoperative Neurophysiological Monitoring on Surgery of High-Grade Gliomas

Theodoros Kombos, Thomas Picht, Athanasios Derdilopoulos, and Olaf Suess

J Clin Neurophysiol 2009; 26: 422-5

J Neurooncol (2010) 100:417–426
DOI 10.1007/s11060-010-0193-x

CLINICAL STUDY – PATIENT STUDY

Surgical treatment of high-grade gliomas in motor areas. The impact of different supportive technologies: a 171-patient series

Andrea Talacchi · Sergio Turazzi · Francesca Locatelli · Francesco Sala · Alberto Beltramello · Franco Alessandrini · Paolo Manganotti · Paola Lanteri · Roberta Gambin · Mario Ganau · Vincenzo Tramontano · Barbara Santini · Massimo Gerosa

FMRI CON NAVIGAZIONE + MONITORAGGIO NEUROFISIOLOGICO
Contribuiscono in modo significativo a migliorare l'EOR

TECNOLOGIE PER MIGLIORARE IL MARGINE DI RE

PIANIFICAZIONE PREOPERATORIA e UTILIZZO DEL NEURONAVIGATORE

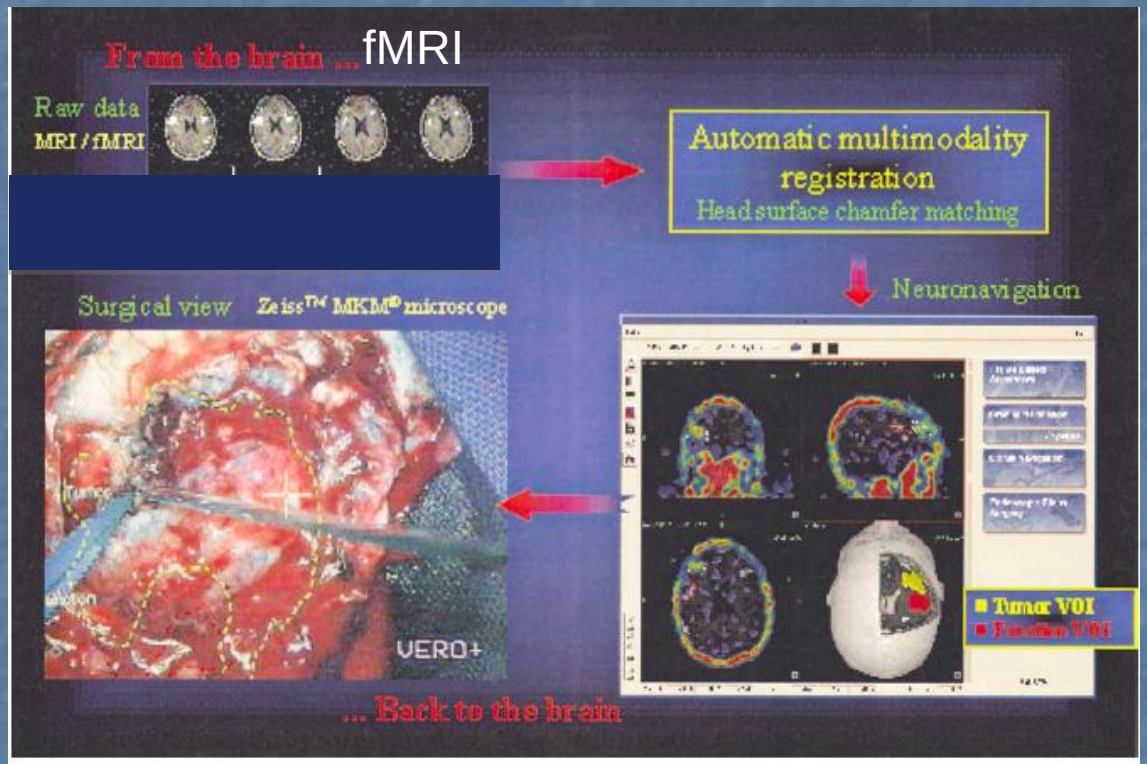
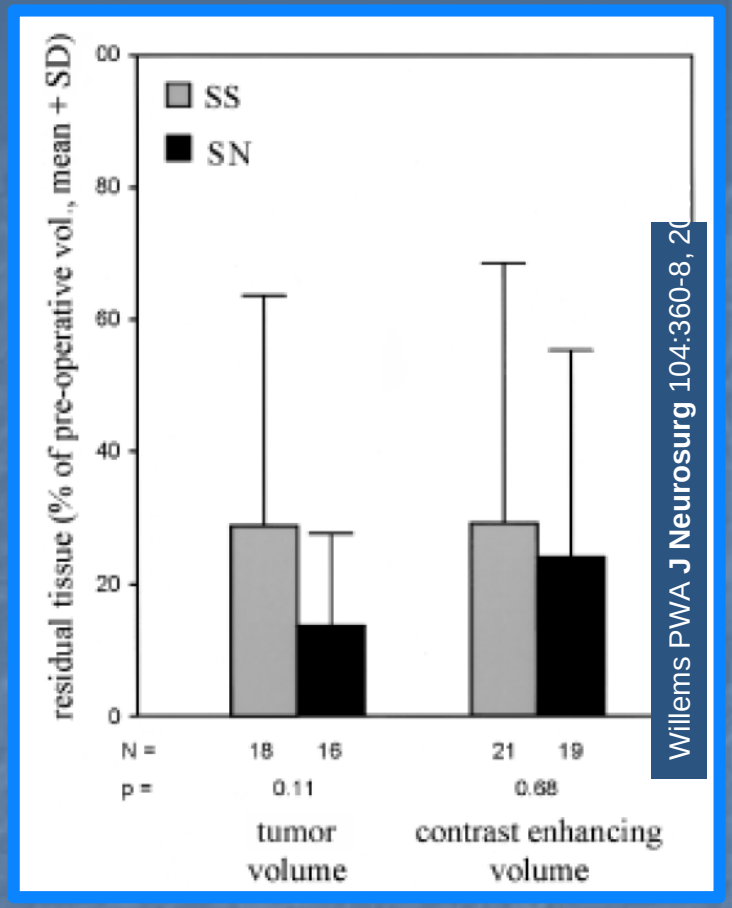


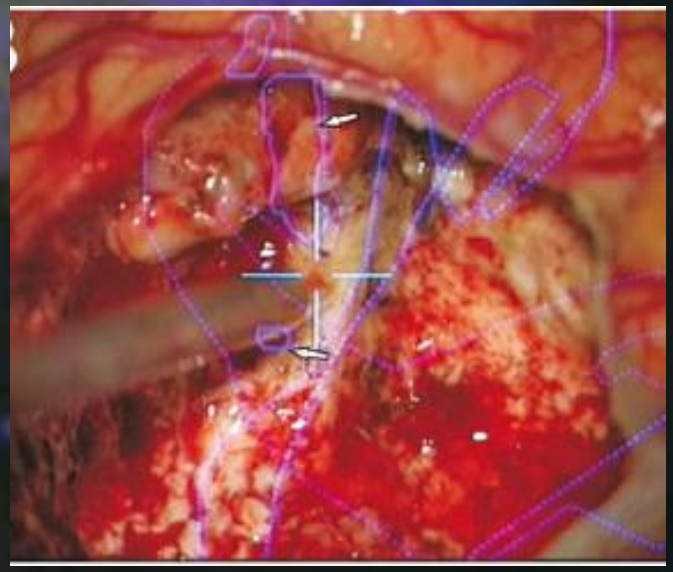
Fig. 3. Whole imaging and operative procedure: four steps done over 24 h (Patient 6). (1) Acquisition of the scintigraphic and anatomical and functional MR data on the morning of the first day. (2) Automatic registration of the images just after completion of the last examination. (3) Neuronavigation: planning of the operation scheduled for the afternoon; during this phase, the surgeon delineates manually the different VOIs around the tumor represented by the thallium fixation and the functional areas located around the tumor; he also determines the best surgical approach to the lesion. (4) Operation the next morning: the image of the microscope is registered with the anatomical MR data given by the external landmarks and the contours of the VOIs are projected into the microscope view along the direction of its optical axis.



5- ALA

IL TESSUTO MALIGNO SINTETIZZA O ACCUMULA DELLE PROTEINE ENDOGENE FOTOSENSIBILIZZANTI DOPO LA SOMMINISTRAZIONE DI ACIDO 5-AMINOLEVULINICO IN ECCESSO.
SI TRATTA DI UN PRECURSORE NATURALE NELLA BIOSINTESI DELL'EME.
APPLICATO ANCHE SUI GLIOMI DALLA FINE ANNI'90.

Stummer W et al. **Neurosurgery** 1998; 42(3) 518-26

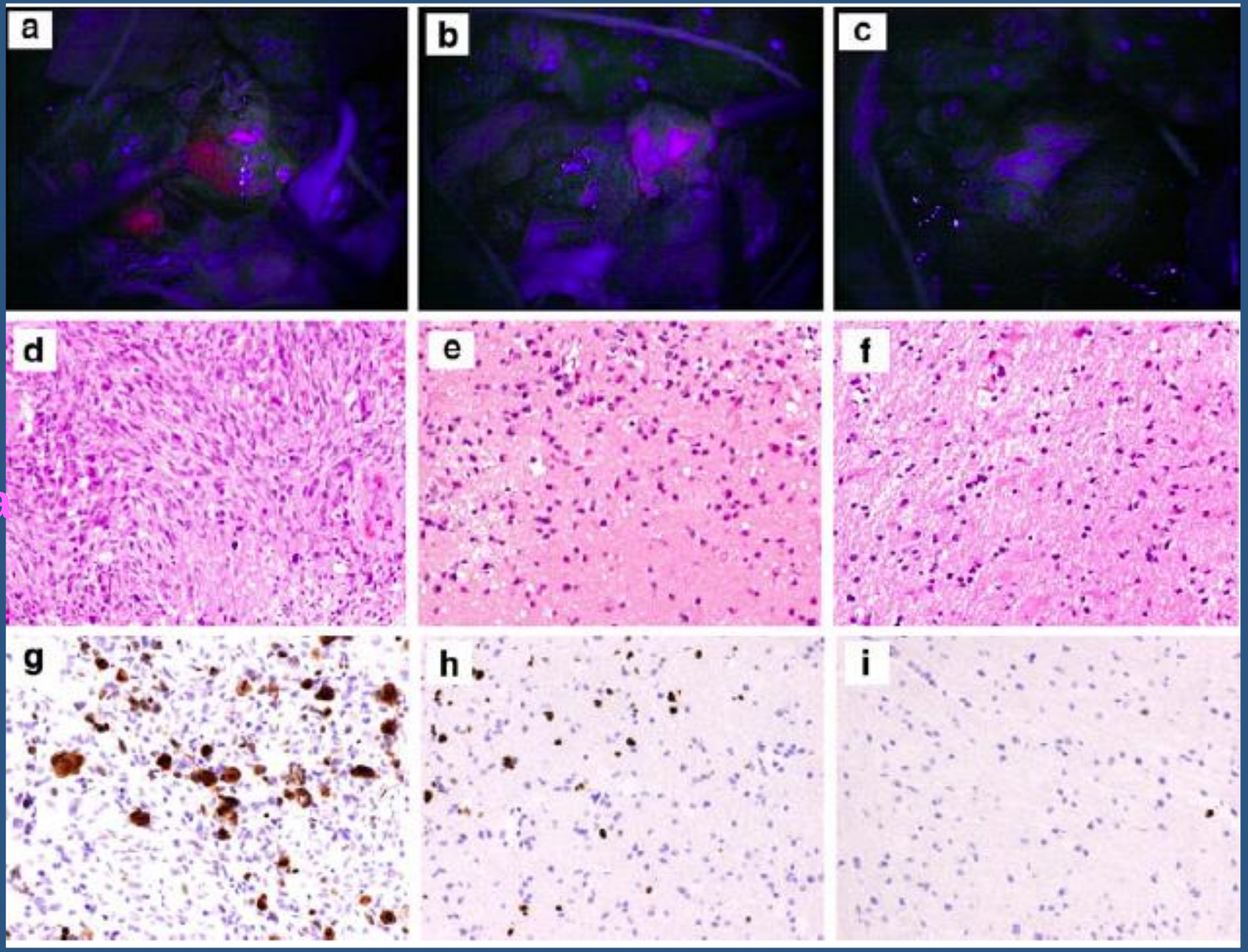


Eyuepoglu IY et al. PLOS one 2012; 7 (9) e44885

5-ALA intraop

H&E istologia

Ki-67



Diez Valle R et al. **J Neurooncol** 2011; 102: 105-13

RMN Intraoperatoria (e DTI) per neuronavigazione and MEP

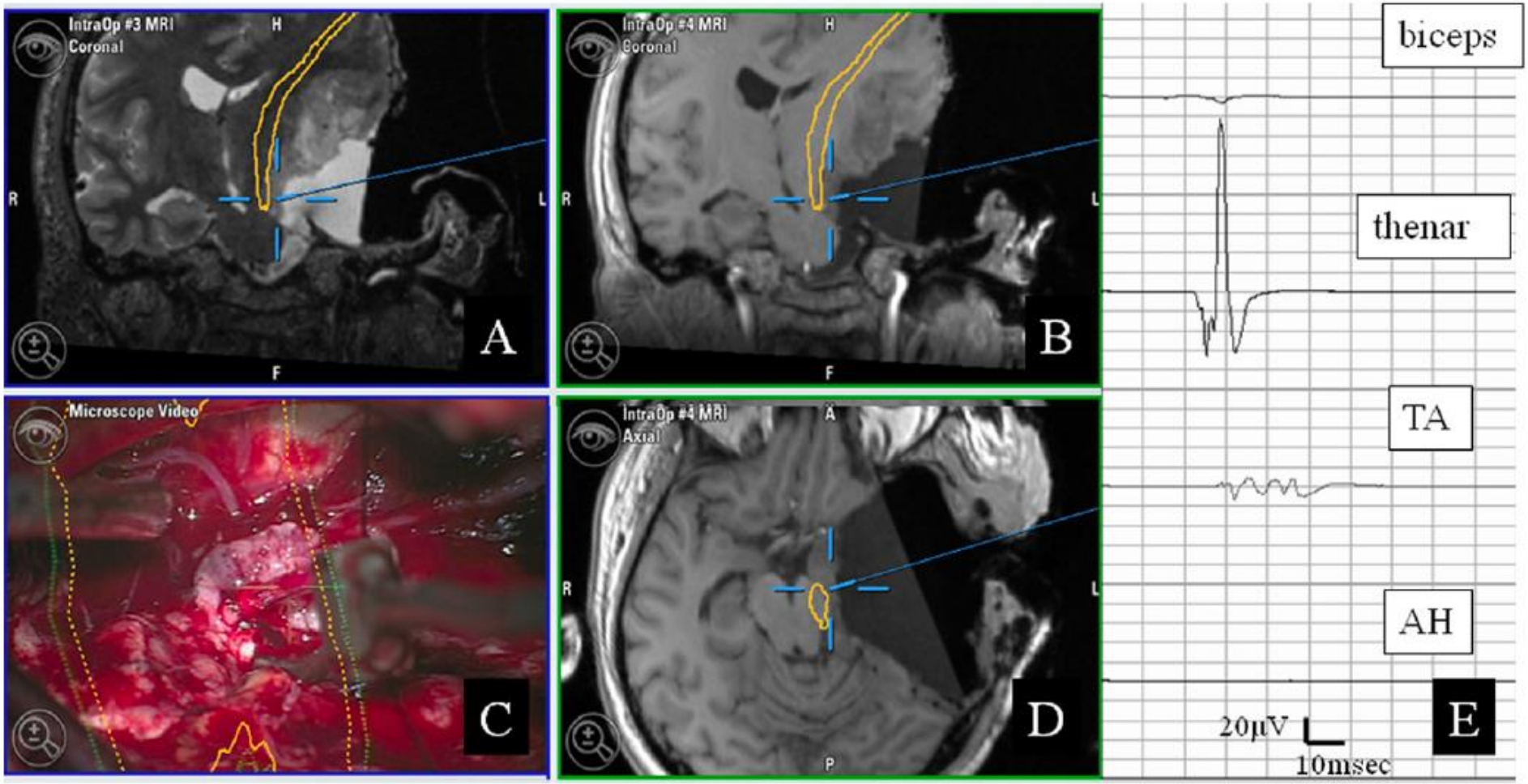
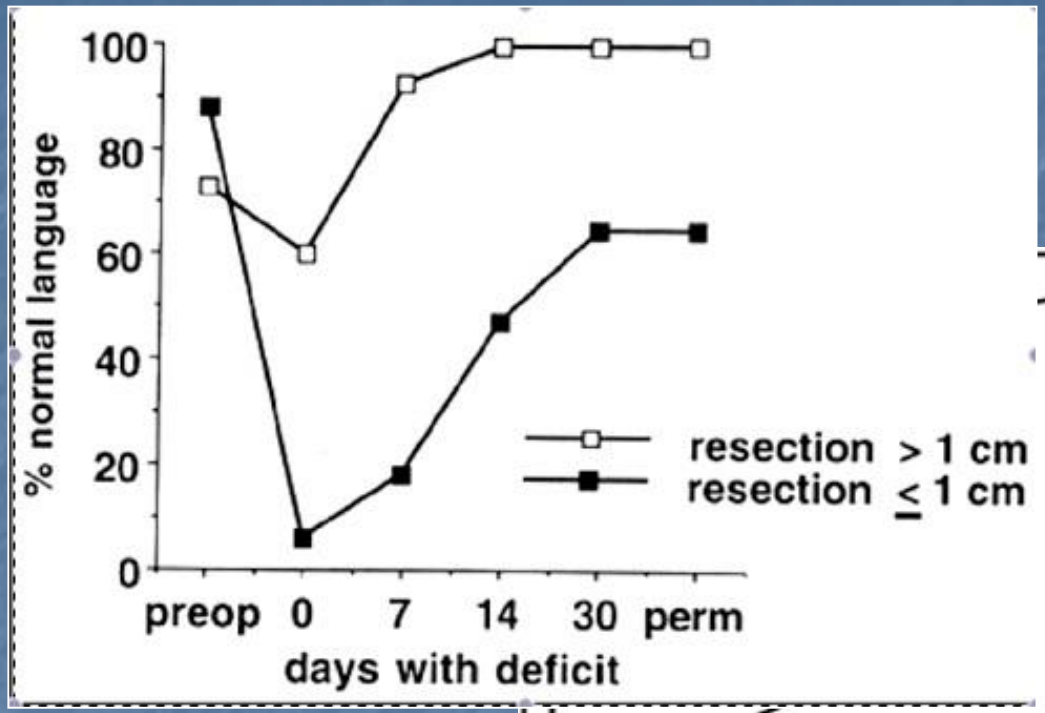
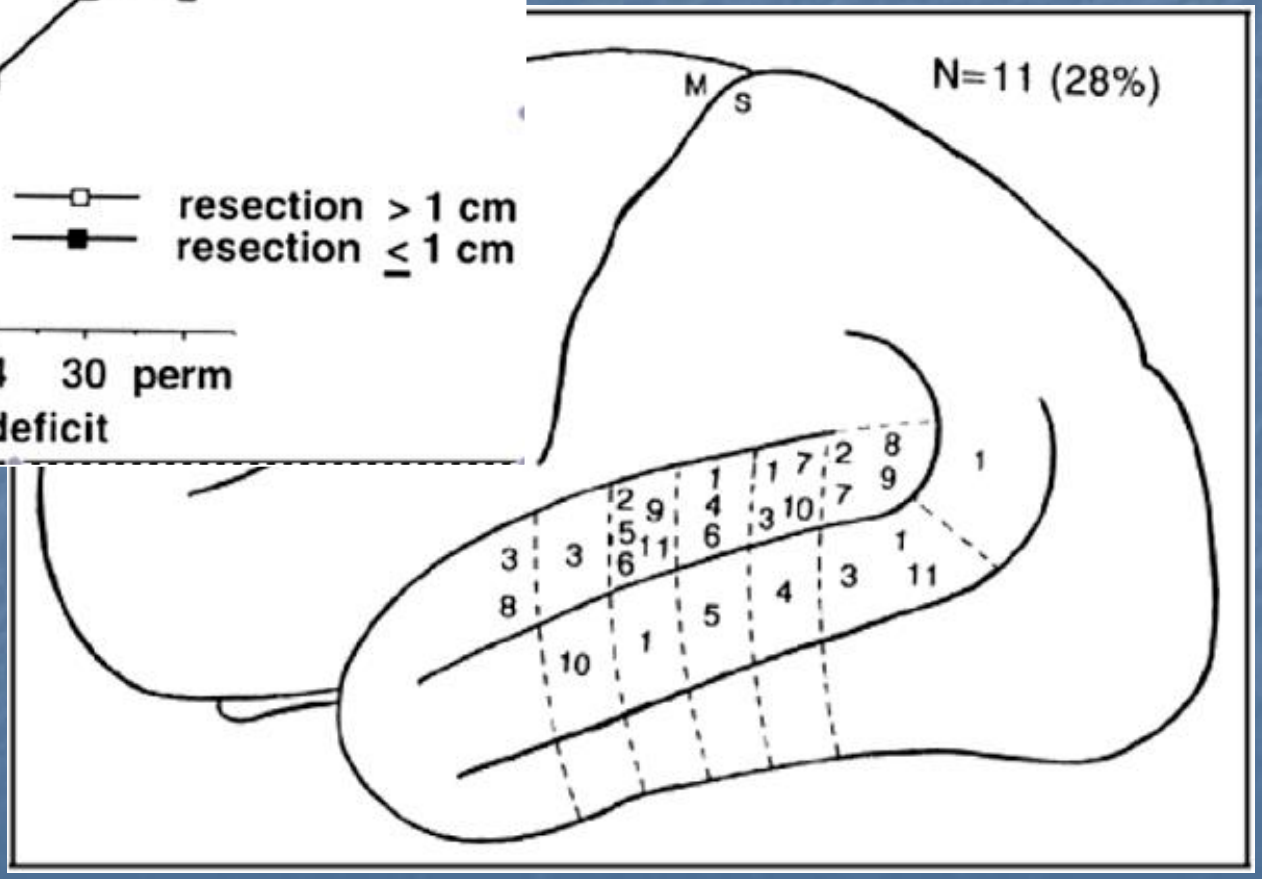


Figure 2. Photographs showing neuronavigation based on intraoperative images (**A,B,D**), a microscopic view with superposed objects (**C**), and associated motor-evoked potential recordings (**E**). The patient had a left temporal glioblastoma. During surgery neuronavigation indicated that intraoperative tractography of the pyramidal tracts (yellow lines) was close to the manipulating field (the center of blue cross). The object of the tracts was superimposed on the surgical field, and the bipolar stimulator was applied at the point where object of the tract was seen. Motor-evoked potential responses were obtained by direct subcortical stimulation. Biceps, biceps brachii muscles; thenar, thenar muscles; TA, anterior tibial muscles; AH, abuductor hallucis muscles.

Maesawa S et al. **World Neurosurgery**; 2010; 74 (1):153-61

MAPPAGGIO INTRAOPERATORIO PER I TUMORI NELL AREA DEL LINGUAGGIO





Risultati peggiori per età più avanzata,
Donne, tumori ad alto grado e tumori estesi
Su due o più quadranti del lobo temporale

…aumenta l'EOR !!!!

Haglund Mi; Berger M; Shamseldin M; Lettich E; Ojemann G. **Neurosurgery** 1994; 34 (4): 567-76

CONTROLLO TAC/RMN SENZA E CON MDC POSTOPERATORIO

The British Journal of Radiology, 84 (2011), 271–278

Clinical target volume delineation in glioblastomas: pre-operative versus post-operative/pre-radiotherapy MRI

[1]P FARACE, PhD, [2]M G GIRI, [2]G MELIADÒ, [3]D AMELIO, MD, [3]L WIDESOTT, [4]G K RICCIARDI, MD, [5]S DALL'OGLIO, MD, [2]A RIZZOTTI, [1]A SBARBATI, MD, [4]A BELTRAMELLO, MD, [5]S MALUTA, MD and [3]M AMICHETTI, MD

[1]*Department of Morphological-Biomedical Sciences, Section of Anatomy and Histology, University of Verona, Italy,* [2]*Medical Physics Department, Borgo Trento Hospital, Verona, Italy,* [3]*ATreP, Provincial Agency for Protontherapy, Trento, Italy,* [4]*Neuroradiology Department, Borgo Trento Hospital, Verona, Italy and* [5]*Radiotherapy Department, Borgo Trento Hospital, Verona, Italy*

La RMN postoperatoria risulta più utile nella pianificazione della RT rispetto a quella preoperatoria

Inoltre ha
- Valore prognostico e
- Serve come feedback ai neurochirurghi

CI SONO ANCHE

ALTRE VARIABILI CHE INFLUENZANO LA SOPRAVVIVENZA,

CHIRURGO ‘INDIPENDENTI’

LA SEDE CORRELA CON LA PROGNOSI

NON SOLO PER LA EOR

Zona Subventricolare

..reclutamento delle staminali residenti da parte del tumore

TIPO I: contatto sia con SVZ sia con corteccia
TIPO II: contatto solo con SVZ
TIPO III: contatto solo con corteccia
TIPO IV: non contatto né con SVZ né con corteccia

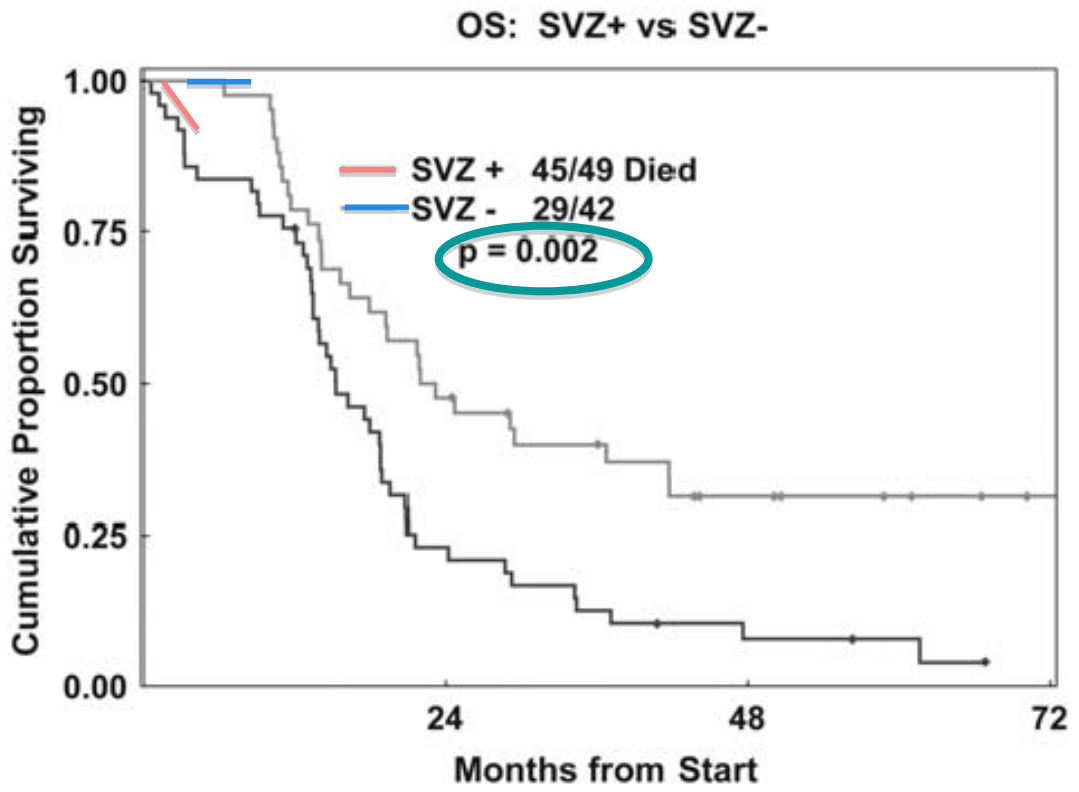
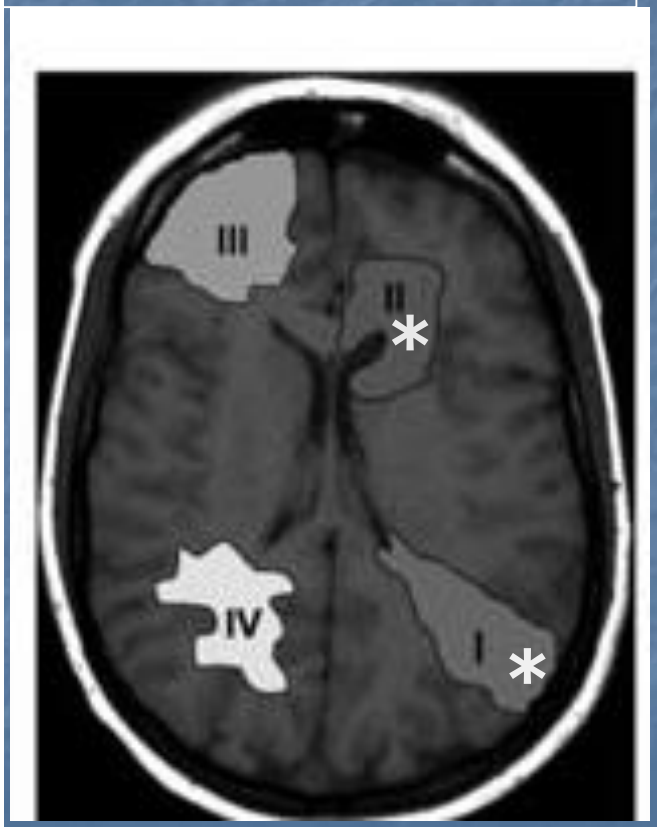


Fig. 6. Kaplan-Meier curve demonstrating survival difference between SVZ-positive and SVZ-negative tumors.



INDIPENDENTEMENTE DALLA EOR.... ... /. **Neuro-Oncology** 2012- UNIV. of S.FRANC

ETA' DEL PAZIENTE

Surgical outcomes for older patients with glioblastoma multiforme: preoperative factors associated with decreased survival

Clinical article

Kaisorn L. Chaichana, M.D.,[1,2,4] Khan K. Chaichana, B.S.,[1,2,4] Alessandro Olivi, M.D.,[1,2,4] Jon D. Weingart, M.D.,[1,2,4] Richard Bennett, M.D.,[3] Henry Brem, M.D.,[1,2,4] and Alfredo Quiñones-Hinojosa, M.D.[1,2,4]

Departments of [1]Neurosurgery, [2]Oncology and [3]Medicine, [4]The Johns Hopkins Neuro-Oncology Surgical Outcomes Research Laboratory, Johns Hopkins University and School of Medicine, Baltimore, Maryland

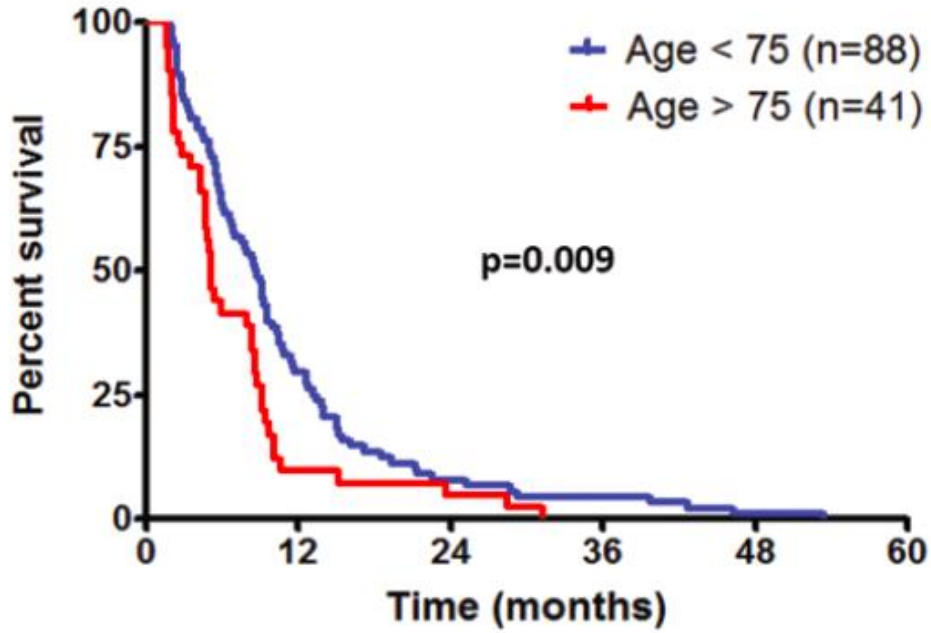


Fig. 2. Survival of patients with intracranial GBM, older and younger than 75 years by age group. Patients younger than 75 years had a median survival of 8.7 months compared with 5.1 months for individuals older than 75 years (p = 0.009).

J Neurosurg 114:587–594, 2011

ALTRE CARATTERISTICHE DEL PAZIENTE

Surgical outcomes for older patients with glioblastoma multiforme: preoperative factors associated with decreased survival

Clinical article

Kaisorn L. Chaichana, M.D.,[1,2,4] Khan K. Chaichana, B.S.,[1,2,4] Alessandro Olivi, M.D.,[1,2,4] Jon D. Weingart, M.D.,[1,2,4] Richard Bennett, M.D.,[3] Henry Brem, M.D.,[1,2,4] and Alfredo Quiñones-Hinojosa, M.D.[1,2,4]

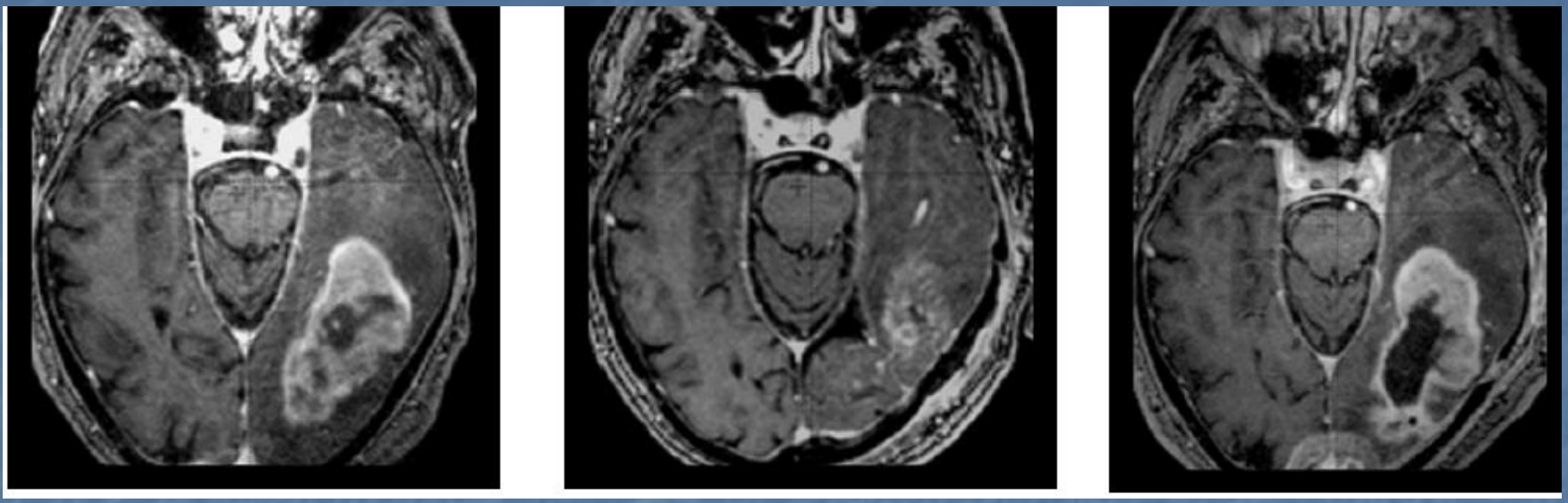
Departments of [1]Neurosurgery, [2]Oncology and [3]Medicine, [4]The Johns Hopkins Neuro-Oncology Surgical Outcomes Research Laboratory, Johns Hopkins University and School of Medicine, Baltimore, Maryland

TABLE 3: Multivariate associations with survival for patients older than 65 years undergoing resection of an intracranial GBM

Multivariate Associations w/ Survival		
Variables	OR (95% CI)	p Value*
factors associated w/ decreased survival		
KPS score <80	1.756 (1.431–2.754)	0.001
COPD	3.762 (1.350–9.061)	0.01
motor deficit	3.480 (1.279–7.993)	0.01
language deficit	2.311 (1.310–3.960)	0.005
cognitive deficit	1.792 (1.089–2.916)	0.02
tumor size	1.189 (1.018–1.358)	0.01
tumor size >4 cm	1.982 (1.264–3.142)	0.002

J Neurosurg 114:587–594, 2011

TRATTAMENTO POSTOPERATORIO



preop postop Pre-RT

DA: Farace P et al. Br J Radiol. 2011 Mar;84(999):271-8. Clinical target volume delineation in glioblastomas: pre-operative versus post-operative/pre-radiotherapy MRI.

Importante il TIMING del trattamento!!!!
Evitare perdite di tempo che si traducono in crescita tumorale

CARATTERISTICHE MOLECOLARI

Quasi ‘classiche’:

MGMT (0-6-metilguanine-DNA-metiltransferasi)

Proteina di riparazione del DNA.
Rimuove l’alchilazione dalla posizione O^6 della guanina
Cioè vanifica la lesione più tossica indotta dagli alchilanti (es. TMZ)
Se il promotore di MGMT è metilato, MGMT non è espresso.

Friedman HS et al. - J Clin Oncol 1998; 16: 3851-7
Esteller et al. NEJM 2000; 343: 1350-4

IDH 1 / 2 (isocitrato deidrogenasi 1 e 2)

La mutazione di questo gene conferisce un vantaggio funzionale alla protiena:
Dovuta ad alterata substrat- specificità
che risulta
in aumentata produzione diD2-isdrossiglutarato (anziché l’alfa ketoglutarato) che
Agisce come oncometabolita

Turcan S et al.- Nature 2012; 483: 479-83

Weller M; Stupp R; et al. **Neuro-Oncology** 2012 iv10

METILAZIONE DEL PROMOTORE MGMT

- omogenea all'interno del glioma
- non cambia durante il corso della malattia (in genere)
- + prognostica nei pazienti con glioma anaplastico
- che ricevono RT o CT o entrambe *(NOA-04, EORTC 26951)*
- utilizzabile come marcatore predittivo per il clinical decision making *:*

  predice il beneficio da CT con agenti alchilanti (EORTC 26981) ed è particolarmente utile nei pazienti anziani con glioblastoma (NOA-08, Nordic trial)

MUTAZIONI DI IDH 1/2

- IDH 1 / 2 spesso espresso nei gliomi di grado II e III e può aiutare nella diagnosi differenziale vs la gliosi reattiva ed altre entità di gliomi (astrocitoma pilocitico, ganglioglioma ed ependimoma che tipicamente non hanno mutazioni IDH 1 /2)
- lo stato IDH 1 / 2 è omogeneo all'interno dei gliomi
- le mutazioni IDH 1 / 2 sono prognosticamente favorevoli, specie nei gradi WHO III

Weller M; Stupp R; et al. **Neuro-Oncology** 2012 iv1

DIAGNOSI:

GLIOMA MALIGNO DIFFUSO CON ASPETTI IMMUNOMORFOLOGICI COMPLESSIVI MEGLIO CONSISTENTI CON

ASTROCITOMA ANAPLASTICO

WHO: grado III. ICD-O code: 9401/3

MICROSCOPIA:

Frustoli di neoplasia gliale con lievi alterazioni da elettroresettore. In essi si osservano densità cellulare di grado moderato, aree microcistiche ed emorragie. Nelle cellule neoplastiche si osserva atipia di grado medio, spesso con singoli elementi più atipici (nucleo angolato, ipercromico e con nucleolo evidente). Sono presenti inoltre vasi a zampa di gallina in assenza di necrosi o proliferazione endoteliale. Le indagini immunoistochimiche hanno mostrato un indice proliferativo, valutato con anticorpo anti-ki67, inferiore al 5% delle cellule neoplastiche.

TMZ e RT

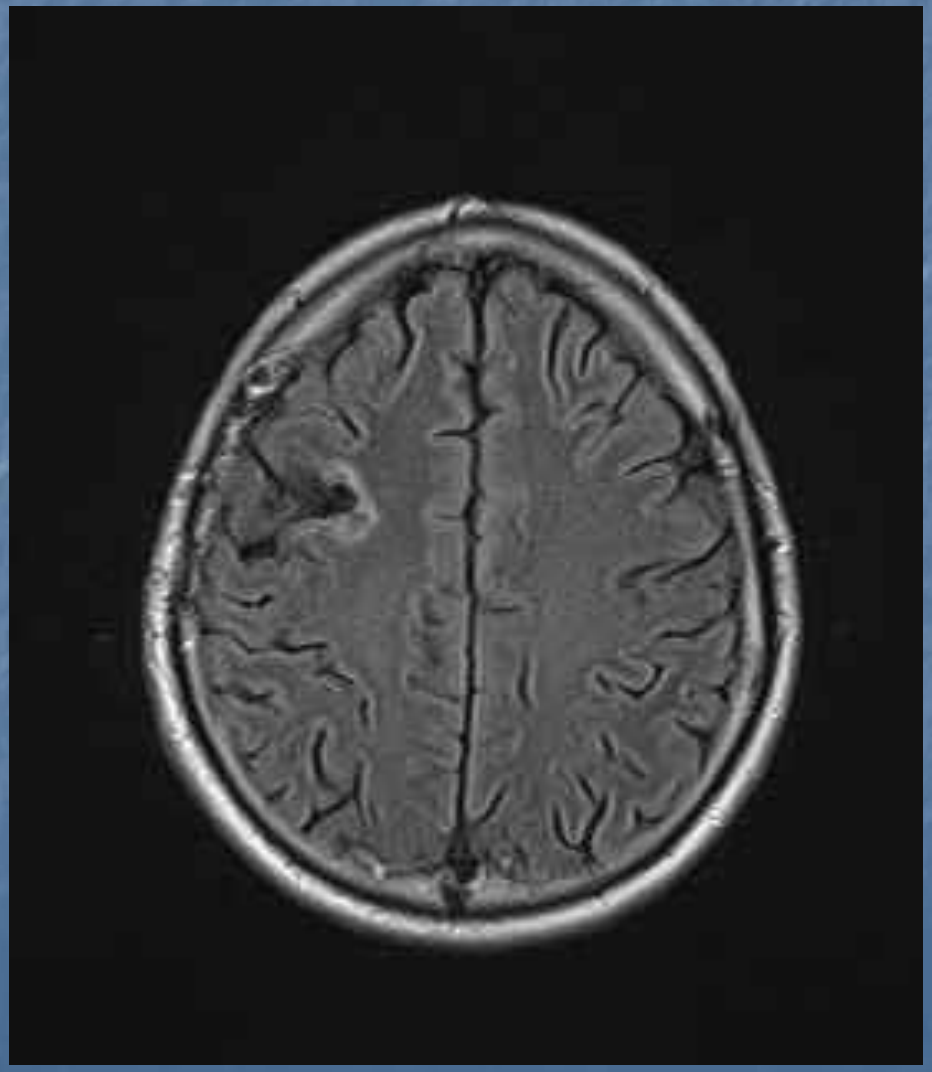
Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

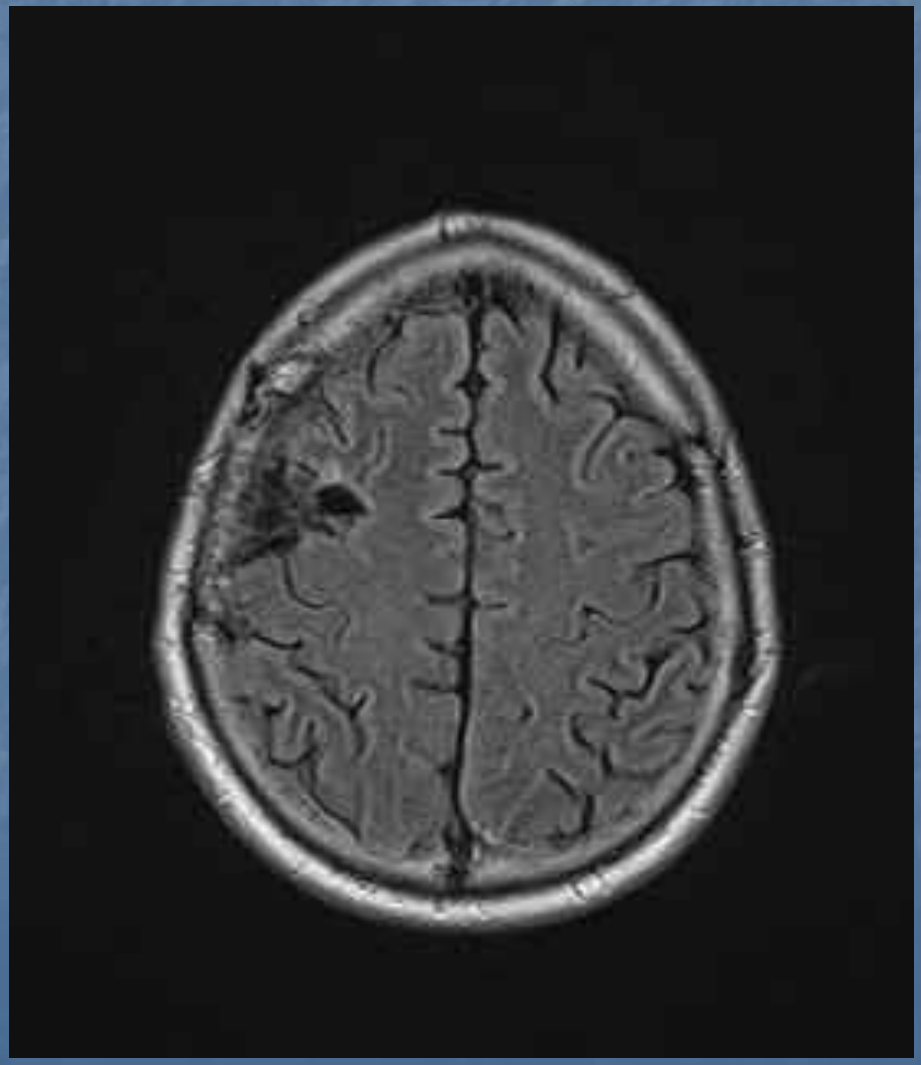
Roger Stupp, M.D., Warren P. Mason, M.D., Martin J. van den Bent, M.D., Michael Weller, M.D., Barbara Fisher, M.D., Martin J.B. Taphoorn, M.D., Karl Belanger, M.D., Alba A. Brandes, M.D., Christine Marosi, M.D., Ulrich Bogdahn, M.D., Jürgen Curschmann, M.D., Robert C. Janzer, M.D., Samuel K. Ludwin, M.D., Thierry Gorlia, M.Sc., Anouk Allgeier, Ph.D., Denis Lacombe, M.D., J. Gregory Cairncross, M.D., Elizabeth Eisenhauer, M.D., and René O. Mirimanoff, M.D., for the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group*

The NEW ENGLAND JOURNAL of MEDICINE

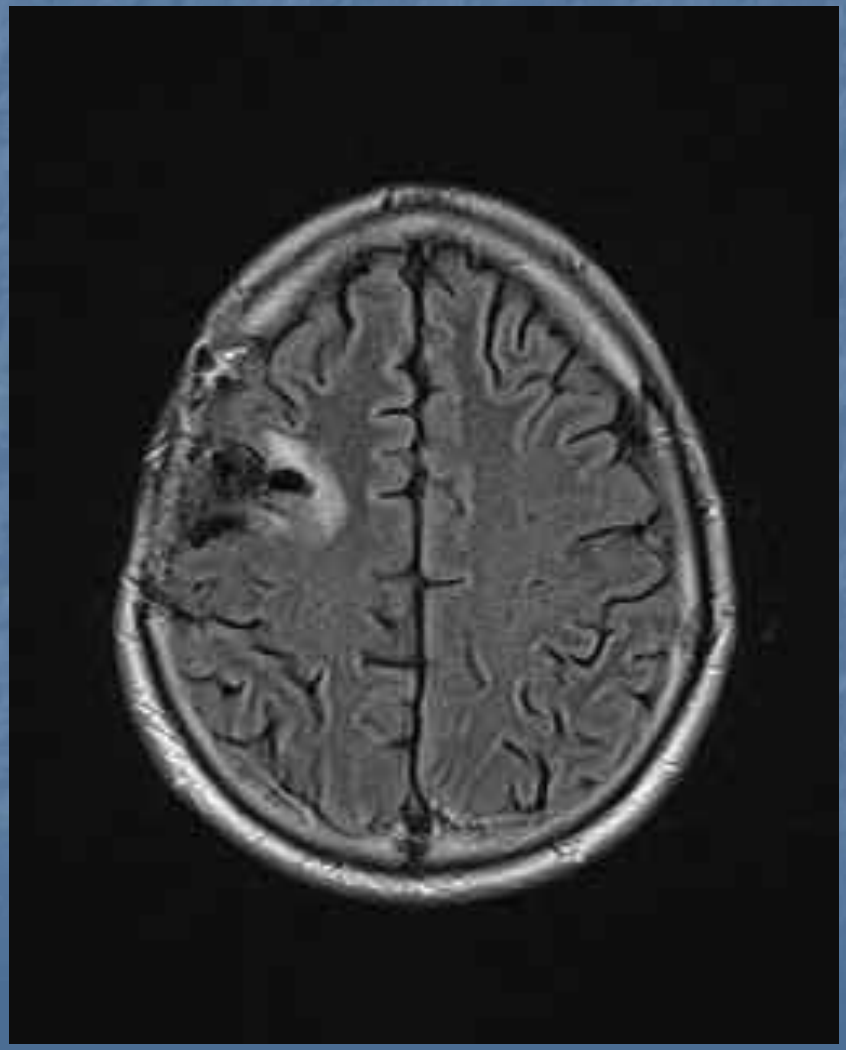
MARCH 10, 2005

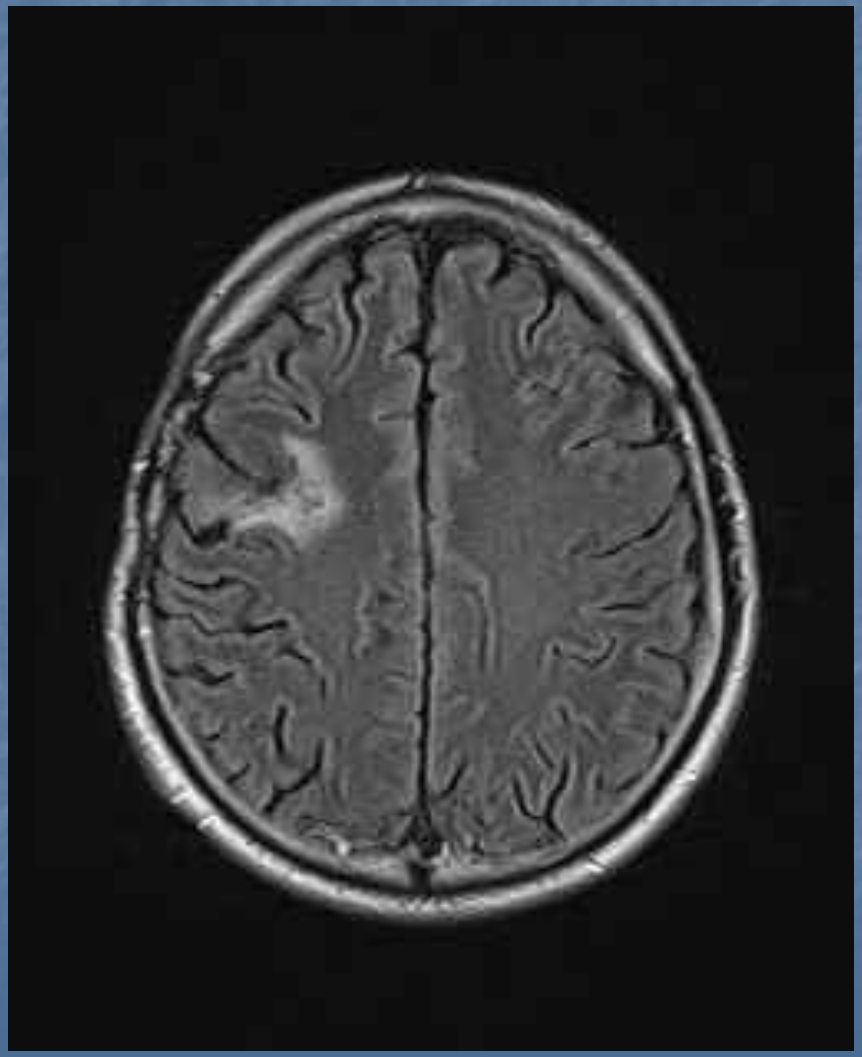
RM a 4 mesi dall'intervento





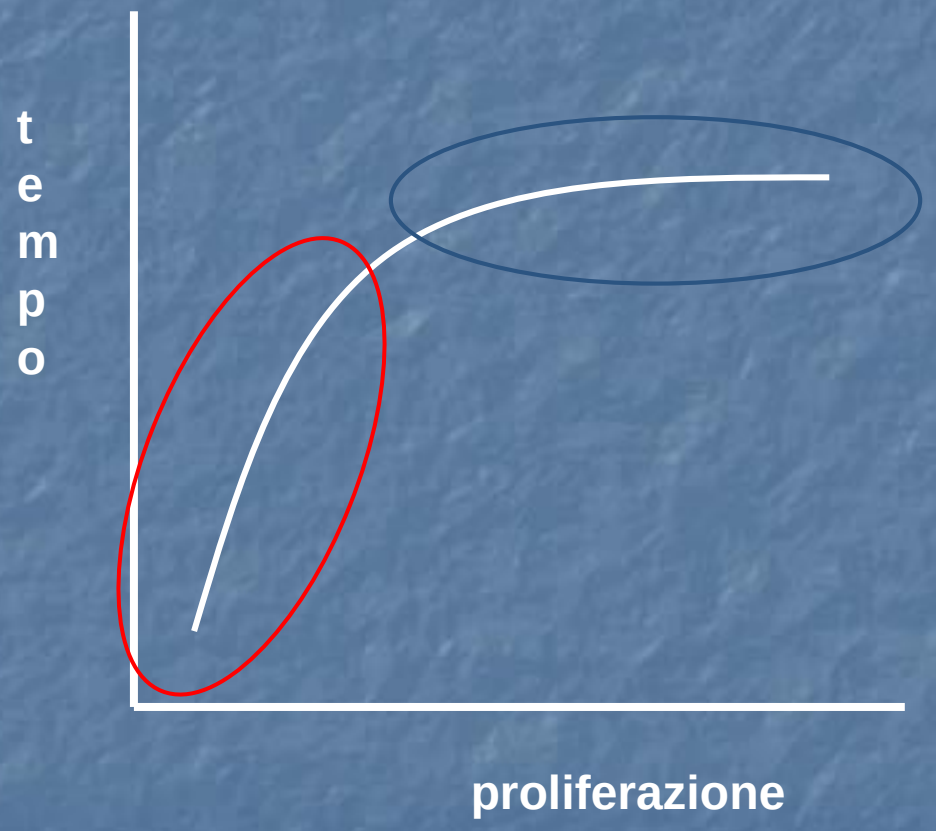
RM a 10 mesi dall'intervento

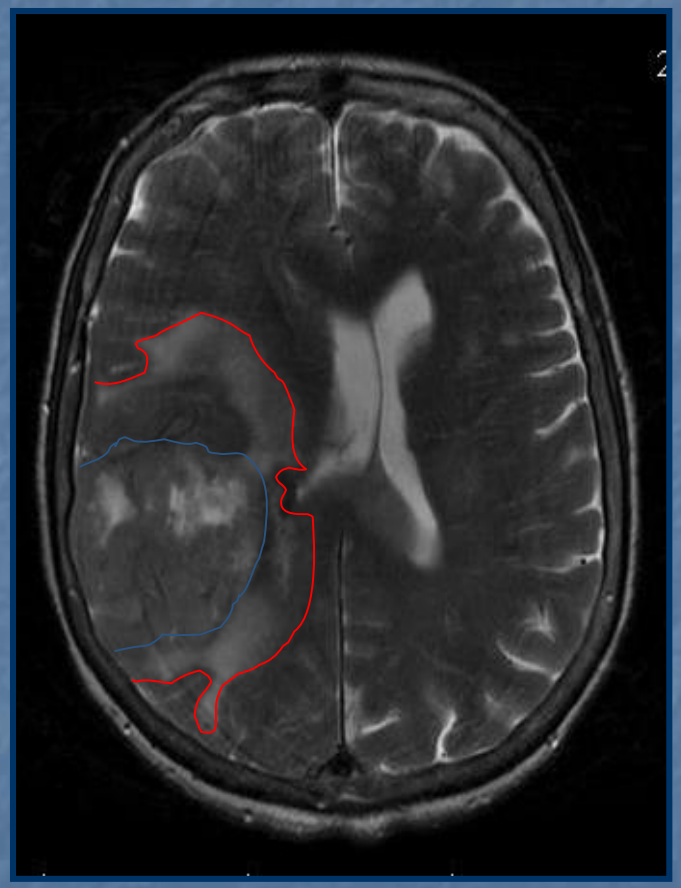




Ruolo della chirurgia

Citoriduzione





Ruolo della chirurgia

Bias

- Eterogeneità e limitatezza dei campioni
- Classificazione
- Definizione dell’estensione della resezione
- Pianificazione e tecnica chirurgica
- Studi retrospettivi e non randomizzati (classe III)

Ruolo della chirurgia

Estensione della resezione chirurgica

"As a prognostic factor in maligant glioma, however, the extent of the surgical resection falls far behind factors over which a surgeon has not control: tumor grade, patient age and KPS score. In some studies, surgery does not even make it onto the radar screen of statistical significance"

Kelly PJ, J Neurosurg, 2004

Ruolo della chirurgia

Estensione della resezione chirurgica

Extent of resection as a prognostic variable in the treatment of gliomas

Hess KR

J Neurooncol 1999, 42: 227-231

Criticism:

Resezione maggiore in aree non eloquenti

differente distribuzione delle covarianti

differenti criteri di classificazione

differente selezione di pazienti

varie "imperfezioni" metodologiche

studi retrospettivi non randomizzati

Studio prospettici randomizzati (Classe evidence I) non eticamente possibili

Ruolo della chirurgia

Estensione della resezione chirurgica

J Neurosurg 99:467–473, 2003

Survival following surgery and prognostic factors for recently diagnosed malignant glioma: data from the Glioma Outcomes Project

EDWARD R. LAWS, M.D., IAN F. PARNEY, M.D., PH.D., WEI HUANG, M.S., FRED ANDERSON, PH.D., ANGEL M. MORRIS, B.S.N., ANTHONY ASHER, M.D., KEVIN O. LILLEHEI, M.D., MARK BERNSTEIN, M.D., HENRY BREM, M.D., ANDREW SLOAN, M.D., MITCHEL S. BERGER, M.D., SUSAN CHANG, M.D., AND THE GLIOMA OUTCOMES INVESTIGATORS

Fattore prognostici favorevoli:

Resezione vs biopsia	*($p < 0.0001$)*
Eta ≤ 60	*($p < 0.0001$)*
KPS ≥ 70	*($p = 0.0004$)*

Studio osservazionale 788 gliomi maligni (Classe evidence II)

Considerazioni finali

- Chirurgia "frustrante"
  - Sopravvivenza invariata nel corso degli ultimi trenta anni, nonostante i progressi della tecnica che hanno ridotto la morbidità
- Qualità di vita (KPS)
  - Entità dell'asportazione proporzionata al danno
- Prognosi legata a markers molecolari e genetici
  - (ampl. EGFR, eterozigosi cromosoma 10 vs 19, MIB-1 etc)
- Trattamento multimodale e terapia traslazionale
  - Team multispecialistico

JM Piepmeyer, Clin Neurosurg, 1998